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Review Article

Hyperglycemic Stress and Carbon Stress in Diabetic Glucotoxicity

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ABSTRACT: Diabetes and its complications are caused by chronic glucotoxicity driven by persistent hyperglycemia. In this article, we review the mechanisms of diabetic glucotoxicity by focusing mainly on hyperglycemic stress and carbon stress. Mechanisms of hyperglycemic stress include reductive stress or pseudohypoxic stress caused by redox imbalance between NADH and NAD^+ driven by activation of both the polyol pathway and poly ADP ribose polymerase; the hexosamine pathway; the advanced glycation end products pathway; the protein kinase C activation pathway; and the enediol formation pathway. Mechanisms of carbon stress include excess production of acetyl-CoA that can over-acetylate a proteome and excess production of fumarate that can over-succinate a proteome; both of which can increase glucotoxicity in diabetes. For hyperglycemia stress, we also discuss the possible role of mitochondrial complex I in diabetes as this complex, in charge of NAD^+ regeneration, can make more reactive oxygen species (ROS) in the presence of excess NADH. For carbon stress, we also discuss the role of sirtuins in diabetes as they are deacetylases that can reverse protein acetylation thereby attenuating diabetic glucotoxicity and improving glucose metabolism. It is our belief that targeting some of the stress pathways discussed in this article may provide new therapeutic strategies for treatment of diabetes and its complications.

Key words: glucotoxicity, carbon stress, diabetes, hyperglycemic stress, reactive oxygen species, redox imbalance, pseudohypoxia

Introduction

Diabetes and its complications are diseases originated from impaired glucose metabolism [1-8]. As glucose metabolism is tightly regulated by insulin, aberrant glucose metabolism can also be regarded as the problems of insulin resistance or insulin deficiency [9-13]. In type 1 diabetes, there is an absolute deficiency or lack of insulin due to β cell destruction [14-16]. But in type 2 diabetes, it is more of an insulin resistance problem, at least at the early stage of the disease [11, 17-20]. As hyperglycemia persists, β cells attempt to secret more insulin to bring down the blood glucose levels [21]. This compensatory mechanism usually can't last long before eventual exhaustion of β cells as β cells cannot keep up with the ever increasing demand imposed by a persistent level of chronic hyperglycemia [22-24]. At this stage, insulin deficiency kicks in because of impaired β cell function, leading to frank type 2 diabetes [10, 21, 25, 26].

Regardless of which type of diabetes, the apparent manifestation of the disease is a high level of blood glucose [15, 27, 28]. While many pathways are activated

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or upregulated to dispose excess glucose, there is a price that the body has to pay, which is deterioration of cell or organ function caused by the toxicity of persistent hyperglycemia [2, 20, 29-32]. This glucose toxicity, often referred to as glucotoxicity, is mediated by many aberrant glucose metabolic pathways or signaling pathways that can eventually lead to cell death [33-36]. In this review article, we summarize these pathways that can be collectively placed under the umbrella of hyperglycemic stress or carbon stress. For hyperglycemic stress, after a brief overview of physiology and pathophysiology of insulin-mediated glucose metabolism, we discuss those stress pathways (Fig. 1) including the polyol pathway that contributes to reductive stress [36], the protein kinase C activation pathway, the hexosamine pathway, the advanced glycation end products (AGEs) pathway, and the enediol pathway that all culminate on oxidative stress [36, 37]. For carbon stress, we first discuss the sources and fates of acetyl-CoA and then expand on protein acetylation and succination [38, 39] that are mainly caused by the elevated levels of acetyl-CoA [40] fueled by increased utilization of fatty acids in diabetes [41]. It is our belief that understanding the mechanisms of hyperglycemic stress and carbon stress may help identify targets for controlling blood glucose levels and thus would benefit for combating diabetes.

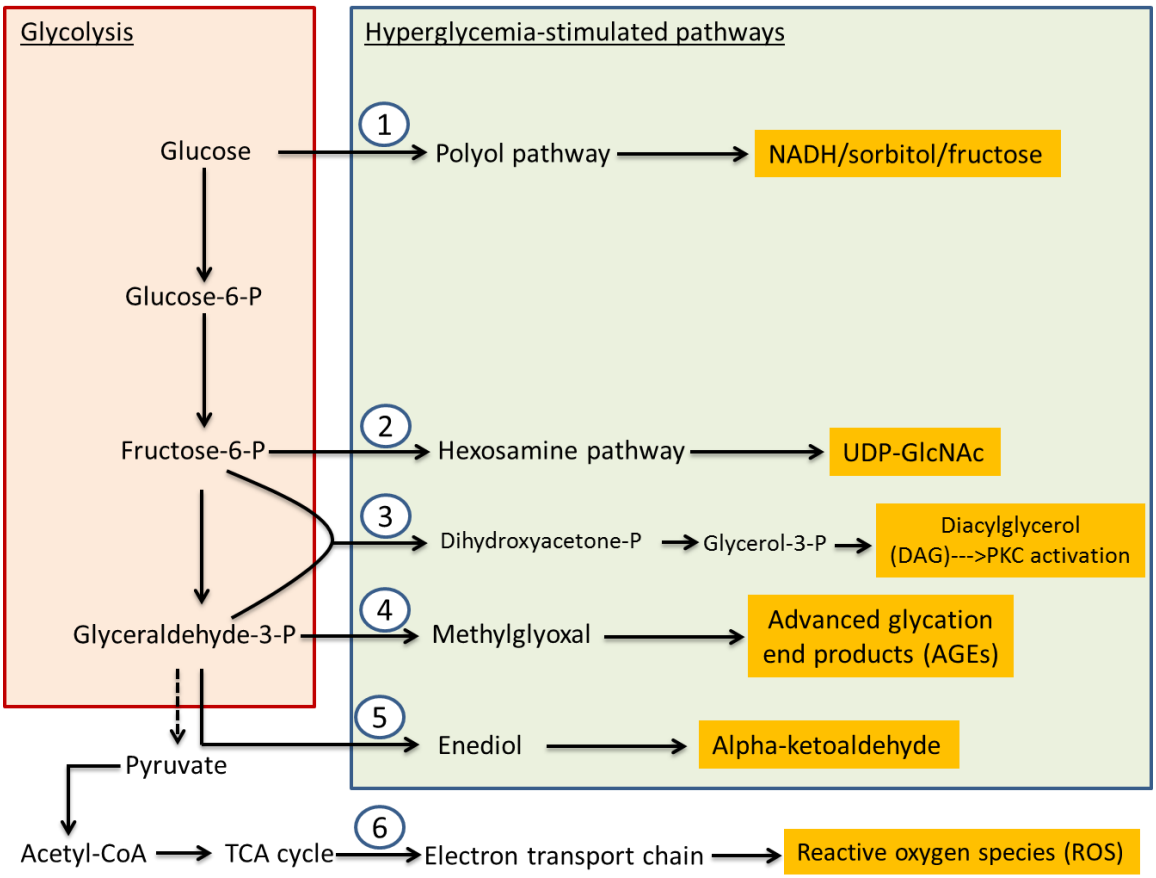

Figure 1. Major pathways upregulated by chronic hyperglycemia. These pathways include the polyol pathway, the hexosamine pathway, PKC activation, formation of advanced glycation end products (AGEs), and the enediol formation pathway. These pathways usually remain dormant under euglycemia conditions whereby majority of the body's glucose is combusted through glycolysis and TCA cycle.

Physiology and pathophysiology of insulin-mediated glucose metabolism

The process of glucose extraction from food is achieved in the gastrointestinal tract [42]. This is followed by release of glucose into the blood stream and glucose stimulation of β cell insulin secretion that promotes uptake of glucose by muscle and adipose tissues [43]. Any surplus glucose will be stored in the form of glycogen in the liver and skeletal muscle, and in the form of fat in adipose tissue (Fig. 2) [43, 44]. Insulin secretion and high level of blood glucose will also suppress gluconeogenesis in the liver, a process that is impaired in diabetes [44-46].

In type 2 diabetes, both muscle and adipose tissues can be insulin resistant, and will not take up more glucose like they do postprandially under euglycemic conditions [44, 47-49]. Interestingly, this phenomenon of resistance has been suggested to be a defense mechanism to prevent glucose toxicity to these tissues [50]. Indeed, diabetic complications in muscle and adipose tissues are very rare [50]. But the inability of these tissues, in particular, muscle, to take up more glucose, is the fundamental problem of glucotoxicity to other organs such as the brain, the kidney, and the lower limbs [51-54].

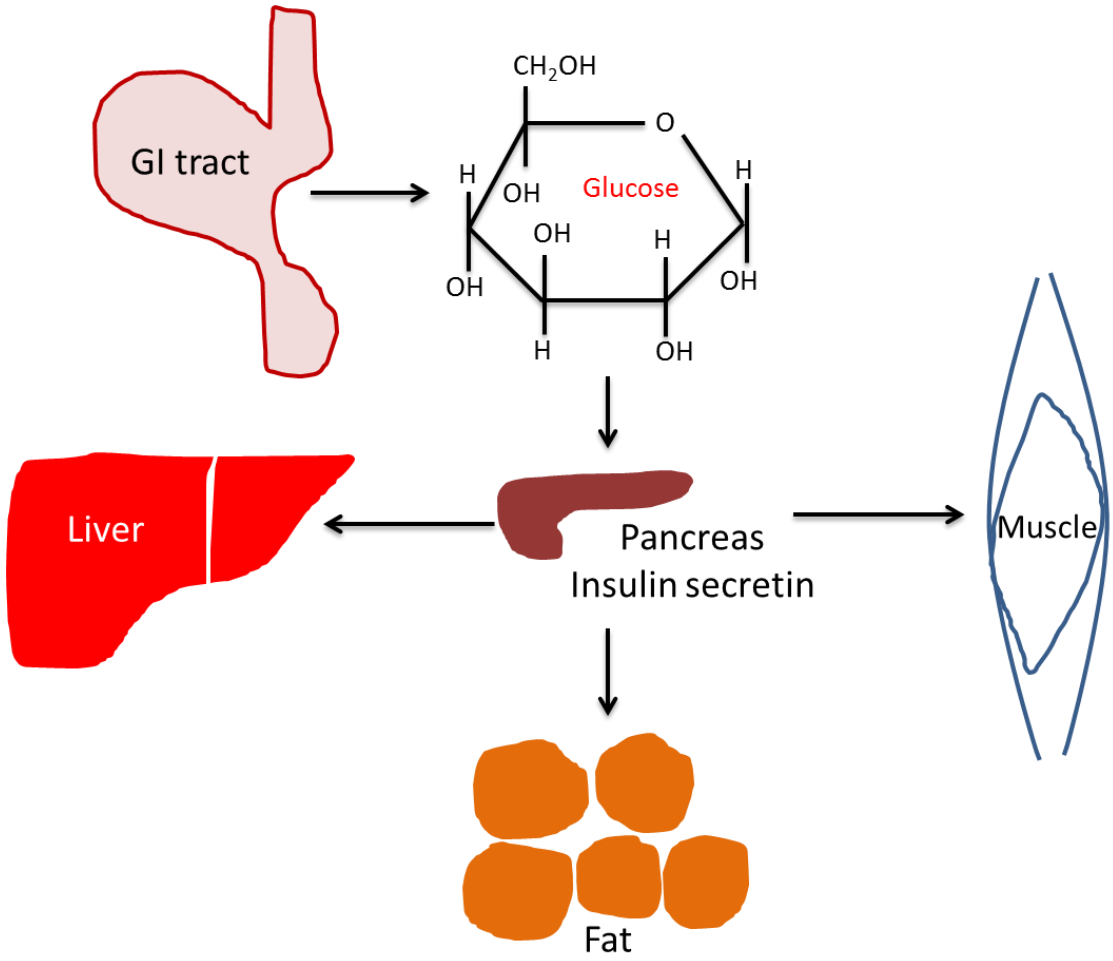

Figure 2. Regulation of glucose homeostasis and pathophysiology of hyperglycemia. Glucose is extracted from food stuff in the gastrointestinal tract and is then released to the blood stream. High level of blood glucose stimulates insulin secretion from islet β cell in the pancreas, leading to uptake of glucose by muscle and adipose tissues. Insulin also suppresses the gluconeogenesis in the liver. Excess glucose is stored in the liver and the muscle as glycogen, and in the adipose tissue as fat. This glucose uptake and storage process and the overall control of glucose homeostasis are impaired in diabetes.

As mentioned above, insulin is tightly linked to glucose metabolism in the body [55-57]. Under normal physiological conditions, insulin stimulates numerous metabolic processes. As shown in Fig. 3, insulin triggers uptake of glucose by muscle and adipose tissue, stimulates fatty acid synthesis from acetyl-CoA, increases the activity of Na^+/K^+ pumps in muscle cells and adipocytes, and promotes glycogen synthesis in muscle and liver [58]. Insulin also promotes gene expression, protein synthesis, and amino acid uptake in all types of cells [58]. However, all these processes are perturbed in diabetes, leading to progressive glucotoxicity [2, 20, 37, 59] that includes hyperglycemic stress and carbon stress as is to be discussed in the following sections.

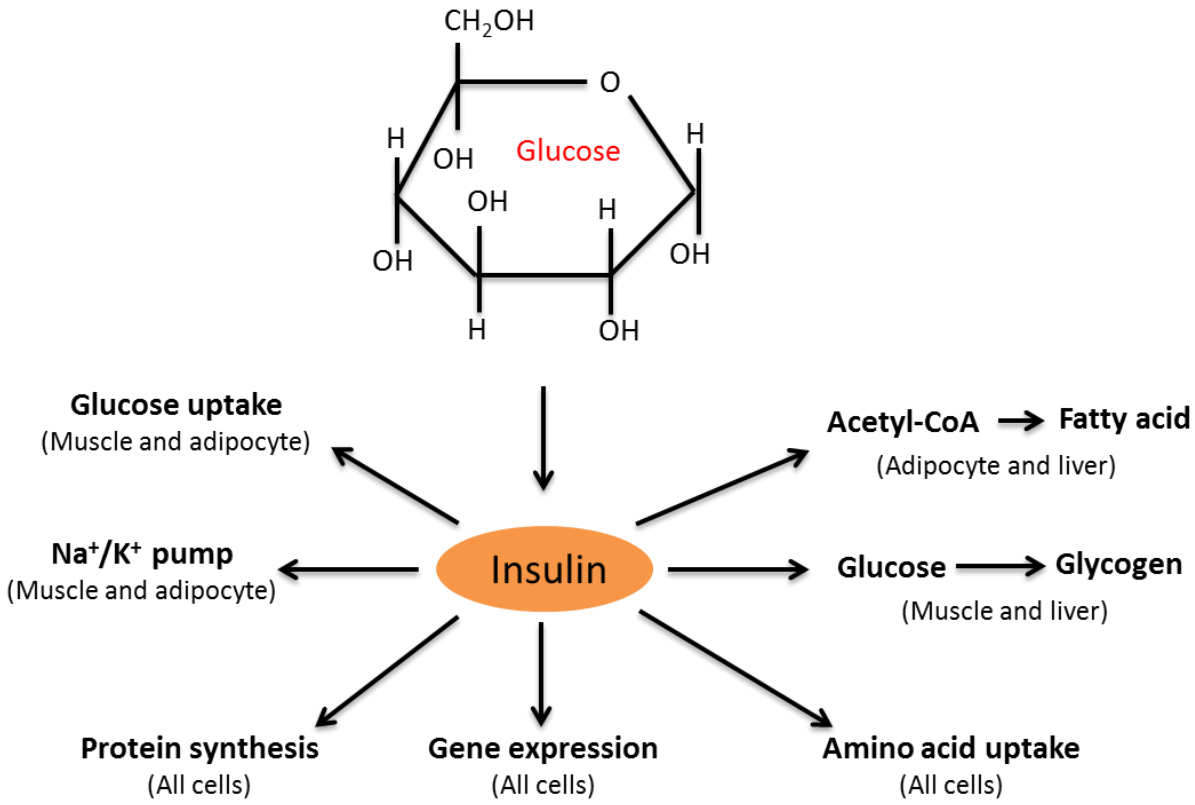

Figure 3. Summary of insulin-stimulated biological processes. Hyperglycemia-induced secretion of insulin can mediate numerous biological processes such as glucose uptake, activation of Na^+/K^+ pumps, synthesis of fatty acid from acetyl-CoA and glycogen from glucose, amino acid uptake, gene expression, and protein synthesis. Figure adapted from reference [58].

A. Hyperglycemic stress

A PubMed search indicates that the concept of "hyperglycemic stress" was first noted in diabetes in 1964 [60]. However, a further search for both "hyperglycemic stress" and "glucotoxicity" returned a zero result, demonstrating that a link between glucotoxicity and hyperglycemic stress has not been clearly and firmly established. Herein, we define hyperglycemic stress as one that mainly encompasses the pathways shown in Fig.

1 that all can be attributed to chronic hyperglycemia in diabetes. The mechanisms of these stresses are all related to elevated levels of ROS production and oxidative stress [37] and hence these stress pathways are highly interrelated.

1. Reductive stress

Reductive stress is defined as excess reducing equivalent in a cell and is usually expressed as an increased ratio between NADH and NAD^+ (or NADPH and $NADP^+$) [36, 61-65]. In chronic hyperglycemic situation, aldose reductase (AR), catalyzing the first reaction in the polyol pathway, is activated [66-69]. AR has a low affinity to glucose and hence is only active at high levels of glucose [54]. AR catalyzes reduction of glucose to sorbitol that is further oxidized to fructose by sorbitol dehydrogenase (the second reaction of the polyol pathway). As shown in Fig. 4, NADPH is consumed and NADH is produced, with accumulation of sorbitol and fructose that can affect cellular osmosis [70, 71]. While the activity of polyol pathway is usually negligible under euglycemic condition, it has been estimated that at least 30% of the body's glucose pool is disposed by this pathway under chronic hyperglycemic conditions [72]. Therefore, NADH level is highly elevated, leading to increased reducing equivalent reflected by an increased ratio between NADH and NAD^+. As NAD^+ level goes lower, cells undergo pseudohypoxia challenges [73-75].

Pseudohypoxia is different from hypoxia in that the former has low levels of NAD^+ in the presence of normal level of tissue oxygen [76, 77] while the latter experiences a lower level of tissue oxygen [78-80]. Regardless, both hypoxia and pseudohypoxia will be manifested by impaired NADH oxidation or impaired NAD^+ regeneration. In this sense, pseudohypoxic stress is equivalent to reductive stress as both are caused by a net decrease in the content of NAD^+ [36, 74], a central molecule involved in metabolism, signal transduction, and stress response [81-84].

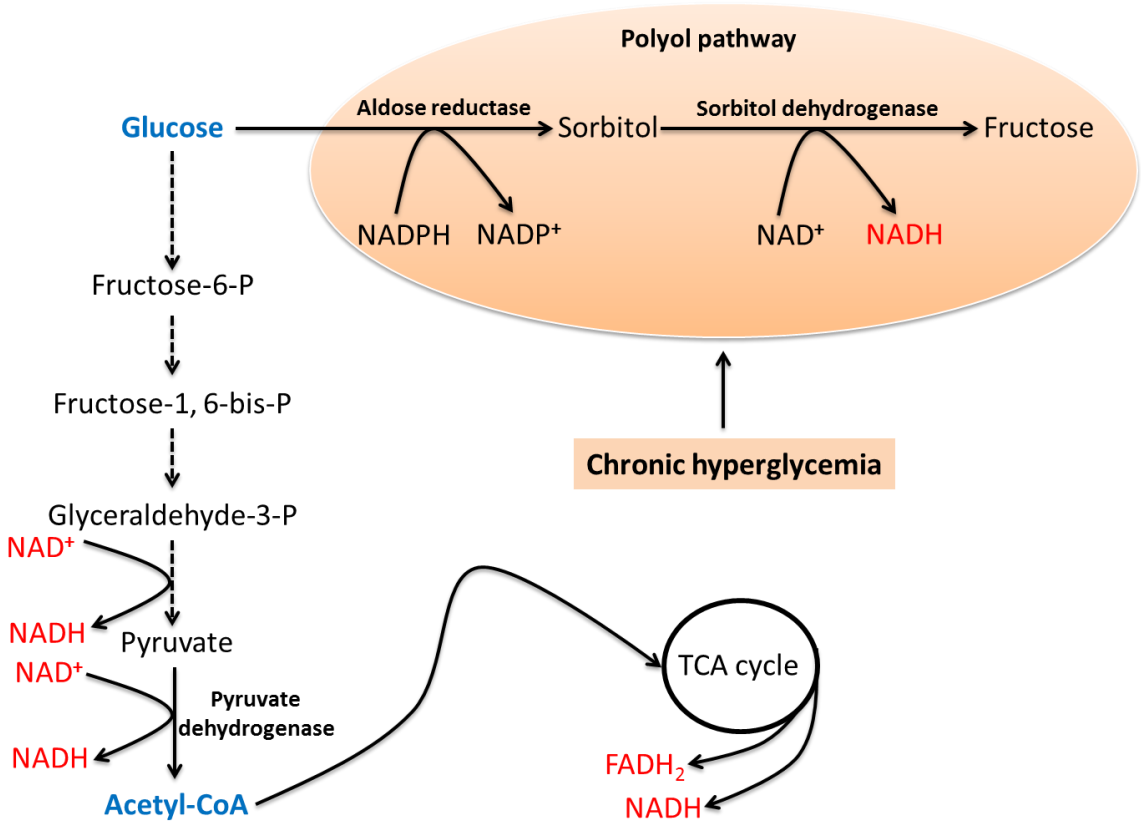

Figure 4. Glucose disposal via the polyol pathway under chronic hyperglycemic conditions in diabetes. This pathway includes two-step reactions. The first one is glucose reduction by aldose reductase to form sorbitol; while the second reaction is sorbitol oxidation by sorbitol dehydrogenase to form fructose. Reducing equivalent is transferred

from NADPH to NADH, leading to elevated level of NADH and reductive stress. The glycolytic pathway is also shown.

Does activation of the polyol pathway lead to depletion of NADPH (the first reaction) in diabetes? This has been repeatedly discussed in the literature and it has been assumed in certain studies that the level of NADPH goes lower in diabetes [85-87], which can diminish GSH content as GSH synthesis requires NADPH [88, 89]. This assumption probably needs to be examined in a tissue dependent manner as it has been reported that in the lens of diabetic rats, NADPH level was not decreased [90]. Moreover, it has been reported that the pentose phosphate pathway that makes NADPH is also upregulated by chronic hyperglycemia [91, 92], leading to a net transfer of excess reducing equivalent from NADPH to NADH [93]. Indeed, it has been demonstrated that NADPH depleted by the polyol pathway can be quickly replenished by the pentose phosphate pathway [64] and potentially by other pathways as well [94]. Therefore, the pentose phosphate pathway in diabetes could also contribute to reductive stress. Hence, reductive stress may be attributed to both the polyol pathway and the pentose phosphate pathway that are activated or upregulated by hyperglycemia in diabetes.

Additionally, as the second reaction of the polyol pathway consumes NAD^+, the polyol pathway can compete for NAD^+ with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [95], potentially down-regulating the glycolytic pathway. This competition, together with the fact that excess NADH will also inhibit GAPDH [67, 96, 97], can lead to more glucose being diverted to the non-conventional pathways as shown in Fig. 1, thereby aggravating glucotoxicity. Given the detrimental effects of the polyol pathway in diabetes, inhibition or disruption of this pathway has been demonstrated to ameliorate diabetes and its complications [98-100].

While there is an oversupply of NADH in diabetes due to persistent hyperglycemia and enhanced fatty acid β oxidation [101-104], there is also likelihood that NAD^+ could be depleted. This is due to the activation of poly ADP ribose polymerase (PARP) by oxidative DNA damage during oxidative stress [105-108]. PARP uses NAD^+ as its substrate and is a nuclear enzyme responsible for DNA repair after damage [109-111]. However, this enzyme, when over-activated, can deplete NAD^+, which is often the case in diabetes [105, 112, 113]. Hence PARP activation has been demonstrated to be involved in cell death [114-117]. That over-activation of PARP contributes to the pathogenesis of diabetes has been further supported by evidence that PARP knockout or deficient animals are protected from chemical-induced diabetes [118-120] and that PARP inhibitors prevent development of diabetes and its complications [121-125].

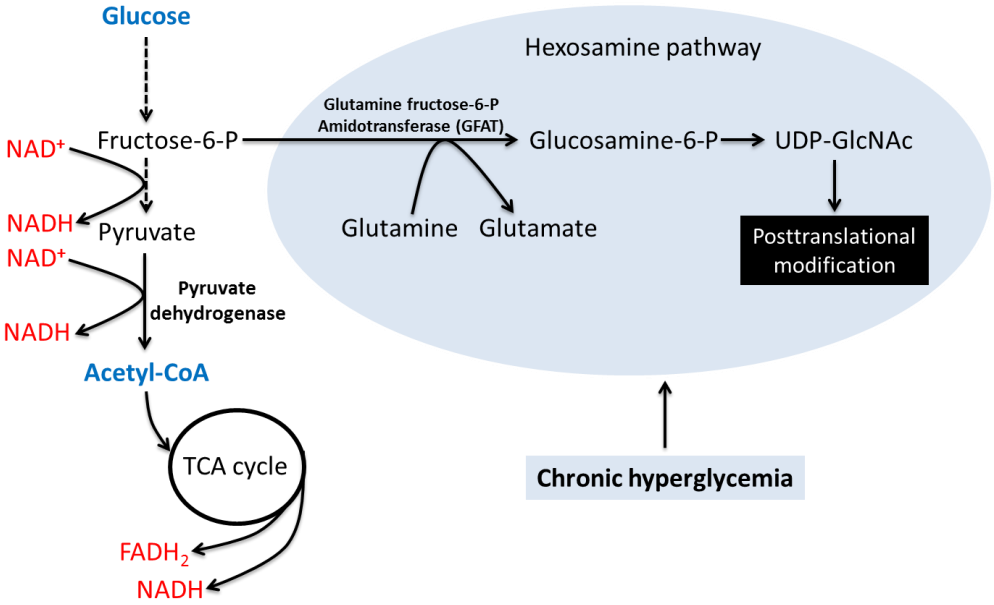

Figure 5. Glucose disposal via the hexosamine pathway. This pathway involves activation of glutamine fructose-6-P amidotransferase that converts fructose 6-P to glucosamine 6-P. This is followed by the

formation of UDP-GlcNAc that is the substrate for protein translational modifications. This pathway is known to be involved in insulin resistance and diabetes. The glycolytic pathway is also shown.

Overall, the toxicity of reductive stress is generally reflected by an increased ratio between NADH and NAD^+ or redox imbalance between NADH and NAD^+, which can impair NAD-dependent enzyme function, deregulate energy metabolism and cell signaling pathways, increase cellular ROS production, and elevates oxidative damage to macromolecules.

2. The hexosamine pathway

As shown in Fig. 5, this pathway originates from fructose-6-P in the glycolytic pathway [126, 127]. It is another pathway that is significantly upregulated by chronic hyperglycemia [126-128]. Fructose-6-P is transformed to glucosamine-6-P by the enzyme glutamine fructose-6-P amidotransferase (GFAT), glucosamine then promotes the synthesis of uridine diphosphate-N-acetylhexosamine (UDP-GlcNAc) that then serves as a substrate for N- or O-glycation of numerous proteins [129, 130]. It should be noted that the mechanism by which hyperglycemia activates GFAT is poorly understood. This posttranslational modification can enhance glucotoxicity by impairing protein function [131, 132] and has been demonstrated to be involved in insulin resistance and pathogenesis of diabetes [133-136].

3. The protein kinase C (PKC) activation pathway

This pathway can originate from either fructose-6-P or glyceraldehyde-3-P in the glycolytic pathway (Fig. 1). The initial species formed is dihydroxyacetone that is further converted to glycerol-3-P. Glycerol-3-P then forms diacylglycerol (DAG) that can activate several isoforms of PKC [137, 138]. PKC then drives numerous signaling processes via protein phosphorylation that regulates signaling protein functions. One of the down-stream targets of PKC is known to be NADPH oxidase whose activation drives superoxide production and thus exacerbates oxidative damage to macromolecules thereby enhancing glucotoxicity [139, 140].

4. The advanced glycation end products (AGEs) pathway

There are two mechanisms by which advanced glycation end products (AGEs) can be formed. The first one is the one shown in Fig. 1 (pathway 4) via the formation of methylglyoxal from glyceraldehyde-3-P [37, 141]. Methylglyoxal then reacts with cysteine, lysine, and arginine residues of proteins, forming advanced glycation end products [142-145]. The second pathway is nonenzymatic, direct attachment of glucose to protein lysine residues via Schiff base formation [53, 146, 147]. The Schiff base then transforms slowly to form stable advanced glycation end products. Many proteins can form AGEs, such as HSP27 [148, 149] and hemoglobin (HbA1c) [27, 150], the quantitation of the latter is often used as an index to measure the progress of diabetes [16]. The glucotoxicity of this pathway has also been demonstrated by observations that the NF-KB signaling pathway can be activated to generate nitric oxide involved in inflammation that can drive the progression of diabetes [151, 152]. Moreover, formation of AGEs can also activate NADPH oxidase [153, 154], leading to superoxide production and oxidative stress. Hence, inhibition of NADPH oxidase could preserve islet β cell functions and lessens glucotoxicity [155-157].

5. The enediol pathway

Chronic hyperglycemia can also elevate the level of enediol, a by-product originated from autoxidation of glyceraldehyde-3-P in the glycolytic pathway [158]. This autoxidation process can generate alpha-ketoaldehyde and ROS, thereby elevating levels of oxidative stress [37]. Formation of enediol has been shown to be involved in pathogenesis of diabetes [159].

6. Oxidative stress

Oxidative stress has been thought to play a central role in the pathogenesis of diabetes and its complications [160-166]. It is induced by overwhelming production of ROS that can attack macromolecules including lipids, DNA, and proteins [28, 167-170]. ROS can be generated by a variety of systems such as mitochondrial electron transport chain [168, 171, 172], d-amino acid oxidase [173-175], dihydrolipoamide dehydrogenase [176-182], α-keto acid dehydrogenase complex [183-187], NADPH oxidase [188, 189], and xanthine oxidase [190, 191]. It should be noted that in the presence of nitric oxide, superoxide can react with nitric oxide to form peroxynitrite [192, 193], a highly reactive species that is known to exert cytotoxicity via modification of macromolecules [194-196] implicated in diabetes [197-201]. Given the role of oxidative stress in diabetes, a variety of antioxidants and phytochemicals have been evaluated for their protective or preventive effects on diabetes and its complications [202-211].

Each of the pathways shown in Fig. 1 can lead to oxidative stress [36, 37]. However, in this section, we would like to focus our discussions on oxidative stress that

is preceded by reductive stress in diabetes [36]. As mentioned above, reductive stress is induced by redox imbalance between NADH and NAD^+. Moreover, excess NADH can overwhelm mitochondrial complex I (NADH-ubiquinone oxidoreductase), a complex that has at least 45 subunits in mammalian cells and serves as the first electron entry point into the mitochondrial electron transport chain [212-216]. As polyol pathway is activated to increase NADH content and poly ADP ribose polymerase is activated to decrease NAD^+ content [36], cells undergo persistent reductive stress as the overall ratio between NADH and NAD^+ is increased [36]. One consequence of this redox imbalance is NADH overload of mitochondrial electron transport chain that is known to be capable of generating most of the ROS under pathological conditions [217, 218]. While the first three complexes (I to III) can all generate ROS via the formation of superoxide anion, complex I would be the major one that makes more ROS under NADH pressure as it is the only site in mitochondria that makes NAD^+ from NADH [219, 220]. Furthermore, an inherent feature of complex I is that the more NADH it oxidizes, the more superoxide it would produce [219, 221]. Therefore, as shown in Fig. 6, complex I could be a pathogenic factor in diabetes [222-224] and could also be a promising target for lowering NADH level and ameliorating reductive stress or oxidative stress [225-229]. In fact, complex I has been the target for metformin in type 2 diabetes, whereby metformin inhibits complex I [230-232], reduces ATP production, and activates AMPK [223, 233-235], leading to improved metabolism in diabetes [236]. Importantly, the action of metformin seems to exert no cellular toxicity, presumably because fuel combustion via complex II can rescue cells from metformin toxicity [237] (Fig. 6).

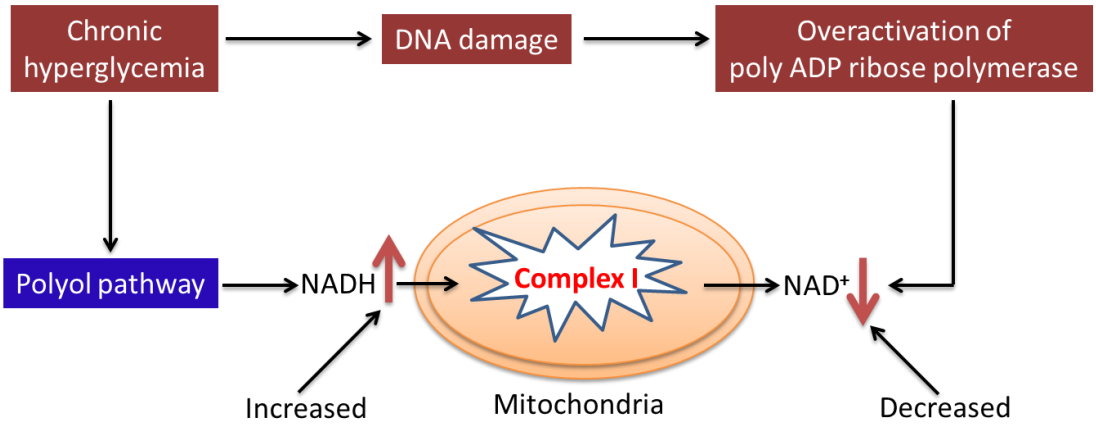

Figure 6. Summary of events leading to redox imbalance between NADH and NAD^+ in diabetes. On one hand, the polyol pathway produces excess NADH; on the other hand, the activation of poly ADP ribose polymerase could potentially deplete NAD^+, leading to great pressure on mitochondrial complex I that is in charge of NADH oxidation and NAD^+ production. NADH overload on complex I can lead to more ROS production. Therefore, complex I could be a pathogenic factor in diabetes and could also be a target for diabetic therapies.

B. Carbon stress

A literature search in PubMed indicates that the concept of carbon stress was first mentioned in 1973 by Hopson and Sack in their studies of changes in cellular phosphorus associated with low carbon stress [238]. In the context of hyperglycemia and diabetes, however, we would like to focus on protein acetylation and succination induced, respectively, by excess acetyl-CoA and fumarate as both forms of posttranslational modifications have been implicated in diabetic glucotoxicity [38, 39, 239, 240]. It should be noted that over-consumption of alcohol can also lead to carbon stress via protein acetylation, which falls beyond the scope of this review [241, 242].

1. Protein acetylation

Excess acetyl-CoA can over-acetylate protein lysine or cysteine residues, leading to protein dysfunction or aberrant protein function [40, 239, 243]. Acetyl-CoA is a central intermediate in metabolism (Fig. 7). On one hand, there are many ways that acetyl-CoA can be produced in a cell. These include pyruvate decarboxylation by pyruvate dehydrogenase complex following glycolysis, β oxidation of fatty acids, deamination and oxidation of amino acids [244]. On the other hand, acetyl-CoA can be used as a source molecule for the synthesis of sterols and fatty acids, can enter into the TCA cycle for complete degradation to H_2O and CO_2, can form ketone bodies after long term fasting or starvation, and can be used as a substrate for modification of proteins, which is a chemical process that is largely independent of enzymes [241, 245-248]. In diabetes, persistent hyperglycemia itself can raise the level of acetyl-CoA, but persistent hyperglycemia can also enhance fatty acid oxidation that can generate a large amount of acetyl-CoA [44]. It is this chronic excess acetyl-CoA that starts attacking proteins via toxic acetylation mechanisms, thereby leading to impairment in protein function, a process contributing to carbon stress [249]. To cope with this carbon stress, cells have evolved mechanisms of detaching the acetyl groups from over-acetylated proteins, which is achieved by a class of enzymes called sirtuins [250-253] (Fig. 8).

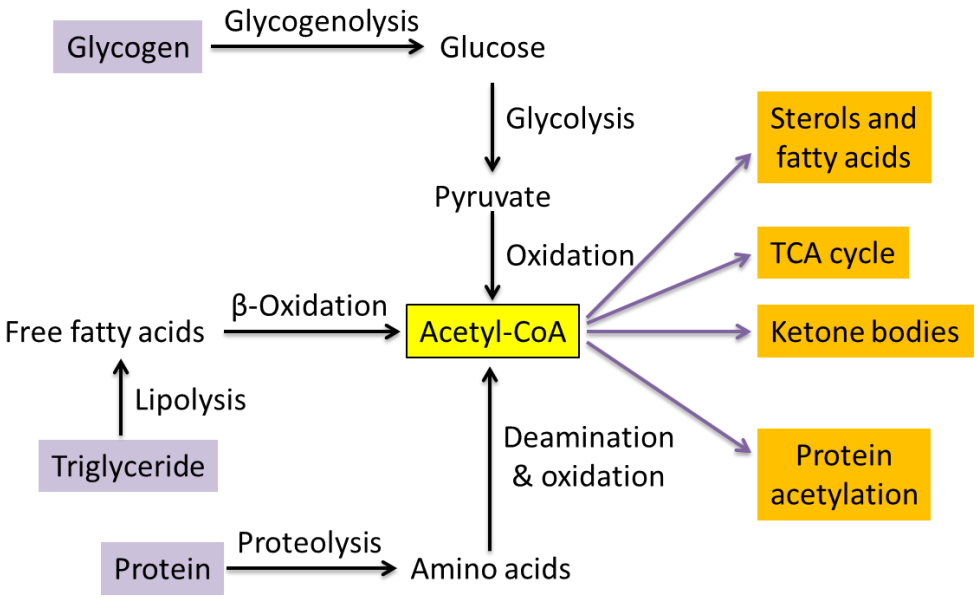

Figure 7. Sources and fates of acetyl-CoA. Acetyl-CoA is mainly generated by combustion of glucose, fatty acid, and proteins. When in excess, acetyl-CoA can be used to make sterols and fatty acids, and can also conjugate to proteins, forming acetylated protein products. In long term fasting or starvation, acetyl-CoA can be used to form ketone bodies that are needed for brain function [288, 289]. Under normal conditions, acetyl-CoA is metabolized to provide energy via TCA cycle and oxidative phosphorylation inside mitochondria.

Sirtuins can be activated under certain stress conditions such as starvation and caloric restriction [254-256] to increase the efficiency of metabolism to cope with metabolic stress. However, sirtuins are usually less active under overnutrition conditions such as diabetes because of overproduction of NADH that can inhibit sirtuins activity [257, 258]. This can make acetylation widespread and toxic in the presence of elevated levels of acetyl-CoA [259, 260]. Therefore, sirtuins have been touted as promising targets for diabetic therapy if their activities can be enhanced [261, 262].

However, sirtuins are NAD^+-dependent deacetylases and are unfortunately usually down-regulated in diabetes [251, 263-267]. If sirtuins have to be upregulated to cope with carbon stress, such approaches will certainly lead to more consumption of NAD^+, the level of which is already low given the activation of poly ADP ribose polymerase and over production of NADH [36]. Therefore, it seems

that upregulation of sirtuins in diabetes will compete for NAD^+ with other NAD^+-dependent enzymes such as PARP and CD38 [105, 268-270] and thus will aggravate the situation of pseudohypoxia. How this can be reconciled needs to be further investigated before sirtuins can be designed as therapeutic targets for diabetes [271, 272].

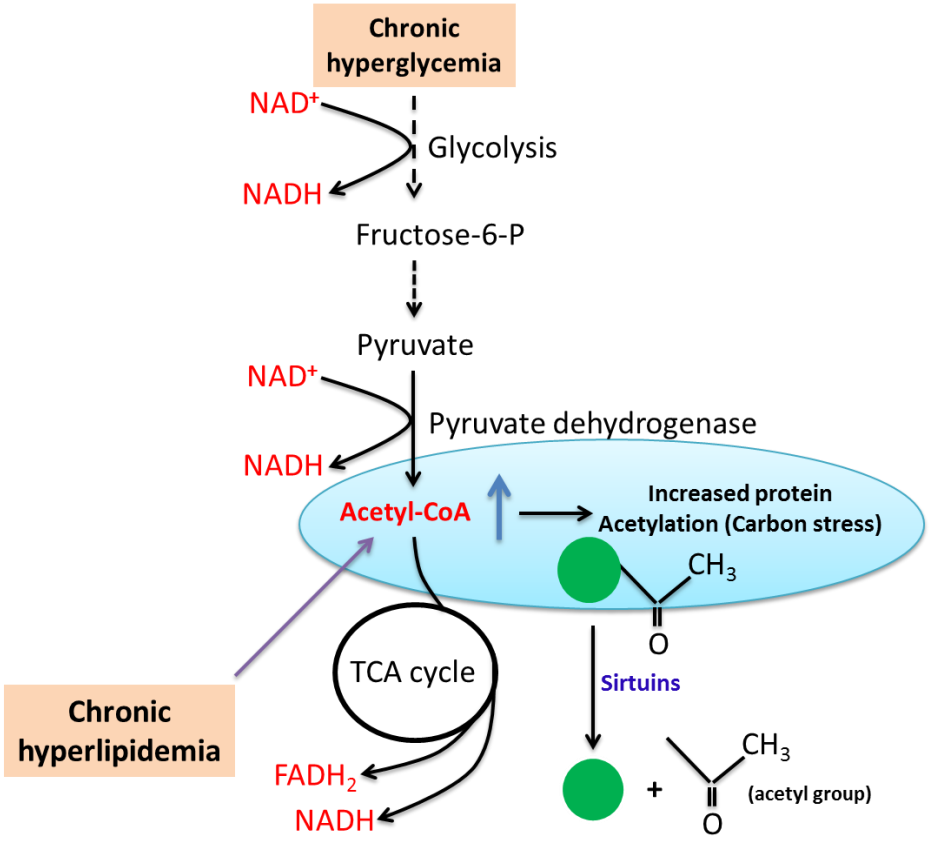

Figure 8. Excess acetyl-CoA produced by hyperglycemia and hyperlipidemia in diabetes can increase nonenzymatic acetylation of proteins via lysine residues. This modification can regulate protein function under stress conditions via sirtuins actions that remove the acetyl groups from the target proteins.

2. Protein succination

Protein succination [39, 273, 274], another form of carbon stress, originates from fumarate [240, 275-277] that is an intermediate in the TCA cycle. When the level of acetyl-CoA is elevated, so is the level of fumarate. Fumarate can then attack protein cysteine residues, resulting in protein succination [240, 278]. Succination can also occur to glutathione [279]. This modification can severely disrupt protein functions given that protein cysteine residues are intricately involved in protein function and redox signaling [280-287]. For example, GAPDH could be inactivated via succination in diabetes [39, 277]. Moreover, in mitochondria, increased succination has been linked to glucotoxicity under hyperglycemia or in diabetes [240]. It should be noted that given the observations that both acetylation of lysine residues and succination of cysteine residues are linked to glucotoxicity, carbon stress may also be placed conceptually under hyperglycemia stress.

Summary and perspectives

In this article, we have reviewed the concept of diabetic glucotoxicity. We classified diabetic glucotoxicity into two categories of stress: hyperglycemic stress and carbon stress. Under hyperglycemic stress, we discussed several mechanisms of glucotoxicity such as reductive or pseudohypoxic stress, the polyol pathway, the hexosamine pathway, the PKC pathway, the AGEs pathway, and the enediol pathway. We emphasize that all the pathways culminate on oxidative stress [37]. As redox imbalance between NADH and NAD^+ is the precursor of oxidative stress [36], we further discussed the role of mitochondrial complex I in glucotoxicity as this complex can produce more ROS in the presence of hyperglycemia and excess NADH and is responsible for mitochondrial regeneration of NAD^+. We think that complex I can be both a pathogenic factor and a potential therapeutic target in diabetes. Under carbon stress, we focused on protein acetylation and succination; both of which can manifest diabetic glucotoxicity. In the context of protein acetylation, we touched on sirtuins that are acetylases capable of improving metabolism by removing acetyl groups off from target proteins. Future in-depth studies targeting these hyperglycemic- and carbon stress pathways may help design novel strategies for treatment of diabetes and its complications.

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Conflict of interests

The authors declare that there is no conflict of interests

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