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Review article

Excessive gluconeogenesis causes the hepatic insulin resistance paradox and its sequelae

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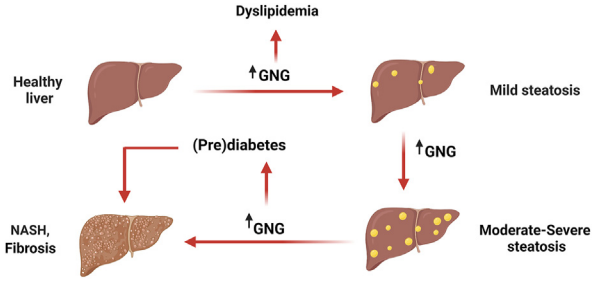
GRAPHICAL ABSTRACT



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ABSTRACT

Background: Hepatic insulin signaling suppresses gluconeogenesis but promotes de novo lipid synthesis. Paradoxically, hepatic insulin resistance (HIR) enhances both gluconeogenesis and de novo lipid synthesis. Elucidation of the etiology of this paradox, which participates in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, the metabolic syndrome and hepatocellular carcinoma, has not been fully achieved.

Scope of review: This article briefly outlines the previously proposed hypotheses on the etiology of the HIR paradox. It then discusses literature consistent with an alternative hypothesis that excessive gluconeogenesis, the direct effect of HIR, is responsible for the aberrant lipogenesis. The mechanisms involved therein are explained, involving de novo synthesis of fructose and uric acid, promotion of glutamine anaplerosis, and induction of glucagon resistance. Thus, gluconeogenesis via lipogenesis promotes hepatic steatosis, a component of NAFLD, and dyslipidemia. Gluconeogenesis-centred mechanisms for the progression of NAFLD from simple steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis are suggested. That NAFLD often precedes and predicts type 2 diabetes is explained by the ability of lipogenesis to cushion against blood glucose dysregulation in the earlier stages of NAFLD.

Major conclusions: HIR-induced excessive gluconeogenesis is a major cause of the HIR paradox and its sequelae. Such involvement of gluconeogenesis in lipid synthesis rationalizes the fact that several types of antidiabetic drugs ameliorate NAFLD. Thus, dietary, lifestyle and pharmacological targeting of HIR and hepatic gluconeogenesis may be a most viable approach for the prevention and management of the HIR-associated network of diseases.

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1. Introduction

Insulin resistance (IR) is a physiological disorder in which insulin target cells become less responsive to insulin. The suppression of gluconeogenesis and stimulation of de novo lipid synthesis are among the effects of hepatic insulin signaling. As expected, hepatic insulin resistance (HIR) promotes excessive gluconeogenesis, which contributes to the development of (pre)diabetes [1]. Paradoxically, HIR also promotes de novo lipid synthesis [2, 3], leading to excessive deposition of fat in the liver (hepatic steatosis) and secretion of very low-density lipoproteins (VLDL) into the blood [4, 5]. Increased incorporation of the newly-synthesized triglycerides into VLDL causes dyslipidemia, which promotes atherosclerosis and cardiovascular disease [4, 6]. Hepatic steatosis is a component of non-alcoholic fatty liver disease (NAFLD), also called metabolism-associated fatty liver disease (MAFLD), which can progress to cirrhosis and hepatocellular carcinoma [7]. NAFLD also predicts (pre)diabetes and vice versa, by mechanisms that are not well-defined [8].

A proper understanding of the etiology of the HIR paradox is important due to its involvement in the above-mentioned diseases. Unfortunately, previously advanced hypotheses do not fully explain it. After a brief discussion of these hypotheses, the current article unmasks a hitherto overlooked pivotal role of HIR-induced gluconeogenesis in promoting de novo lipid synthesis.

2. Strengths and weaknesses of current hypotheses on the HIR paradox

As shown in Figure 1, the binding of insulin to its receptor leads to the successive activation of insulin receptor substrates 1 or 2 (IRS1/2), phosphatidyl inositol-3 kinase (PI3K), and protein kinase B (akt). Akt inhibits forkhead box protein O1 (Foxo-1), a transcription factor which induces the expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) [5, 9]. On the other hand, akt activates the mammalian target of rapamycin complex 1 (MTORC-1), which upregulates the sterol response element binding protein 1c (SREBP-1c), a master inducer of genes involved in lipogenesis, such as acetyl-CoA carboxylase (ACC), ATP-citrate lyase (ACLY), fatty acid synthase, and stearoyl-CoA desaturase [5, 9].

One of the previously advanced explanations for the HIR paradox is that akt more readily activates MTORC-1 than it inhibits Foxo-1, so that residual akt activity in HIR causes de novo lipogenesis but fails to inhibit gluconeogenesis [5]. However, it is unlikely that residual akt activity can induce greater lipogenesis that normal akt activity.

NAFLD is characterized by fasting hyperinsulinemia, which downregulates hepatic IRS2 but not IRS1, and a second hypothesis considers that sustained expression of IRS1 and hyperinsulinemia account for the excessive lipogenesis [10]. However, a recent study found that in individuals with NAFLD, de novo hepatic lipid synthesis was lowest after the ingestion of glucose (when both insulin and glucose levels are highest), casting doubt on such a possibility [11].

Another hypothesis is that endoplasmic reticulum stress (ER stress) in insulin resistant hepatocytes promotes de novo lipogenesis by inducing proteolytic maturation of SREBP-1c independently of insulin [12, 13]. However, ER stress promotes insulin resistance [14], and should thus inhibit akt-induced SREBP-1c activation. Moreover, ER stress induces the maturation and nuclear translocation of the ER-localized protein, cAMP response element binding protein H (CREBH) [15], which upregulates the SREBP-1c inhibitor, insulin-induced gene 2 (insig 2) [16].

Several studies have reported that Foxo-1 induces not only gluconeogenesis but also lipogenesis [17, 18, 19], which fits perfectly with the paradox. Foxo's lipogenic effect was attributed to autophagy [18], or to the activation of MTORC-2, which subsequently induces the activation of akt, glucokinase and SREBP-1c (Figure 2) [17]. The dual-specificity tyrosine phosphorylation–regulated kinase 1B (*DYRK1B*) also promotes

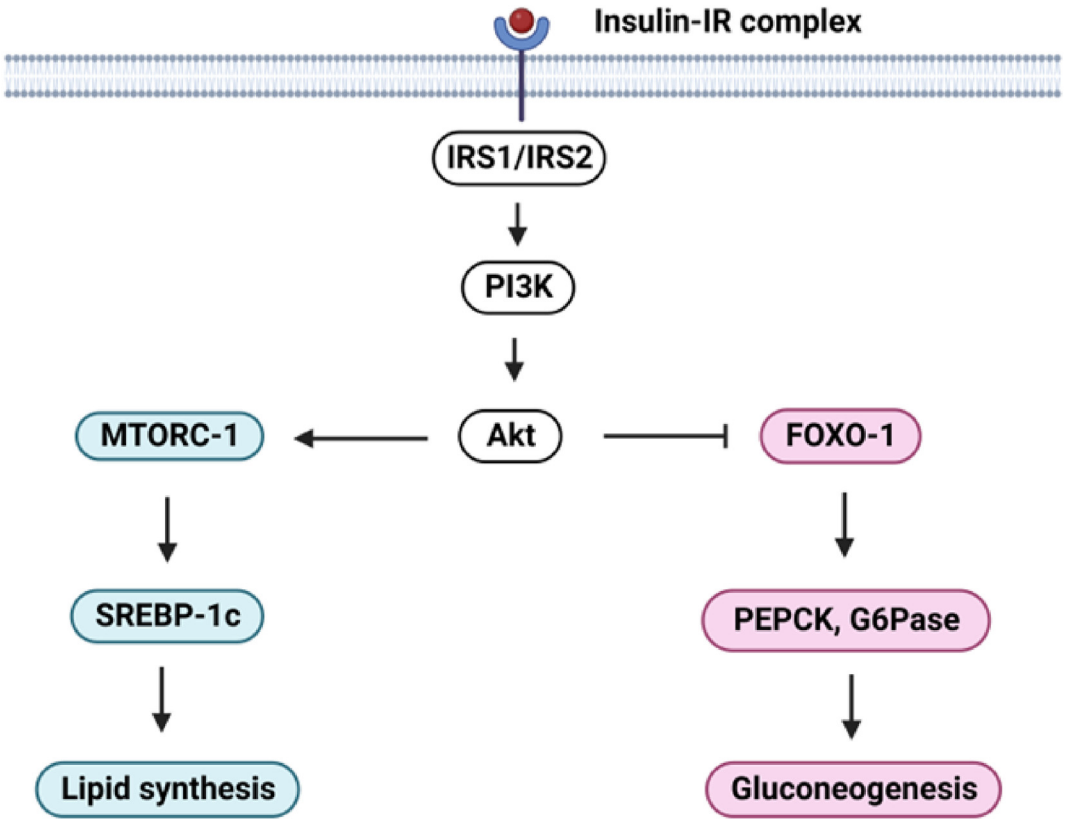

Figure 1. The classical insulin signaling pathway in hepatocytes.

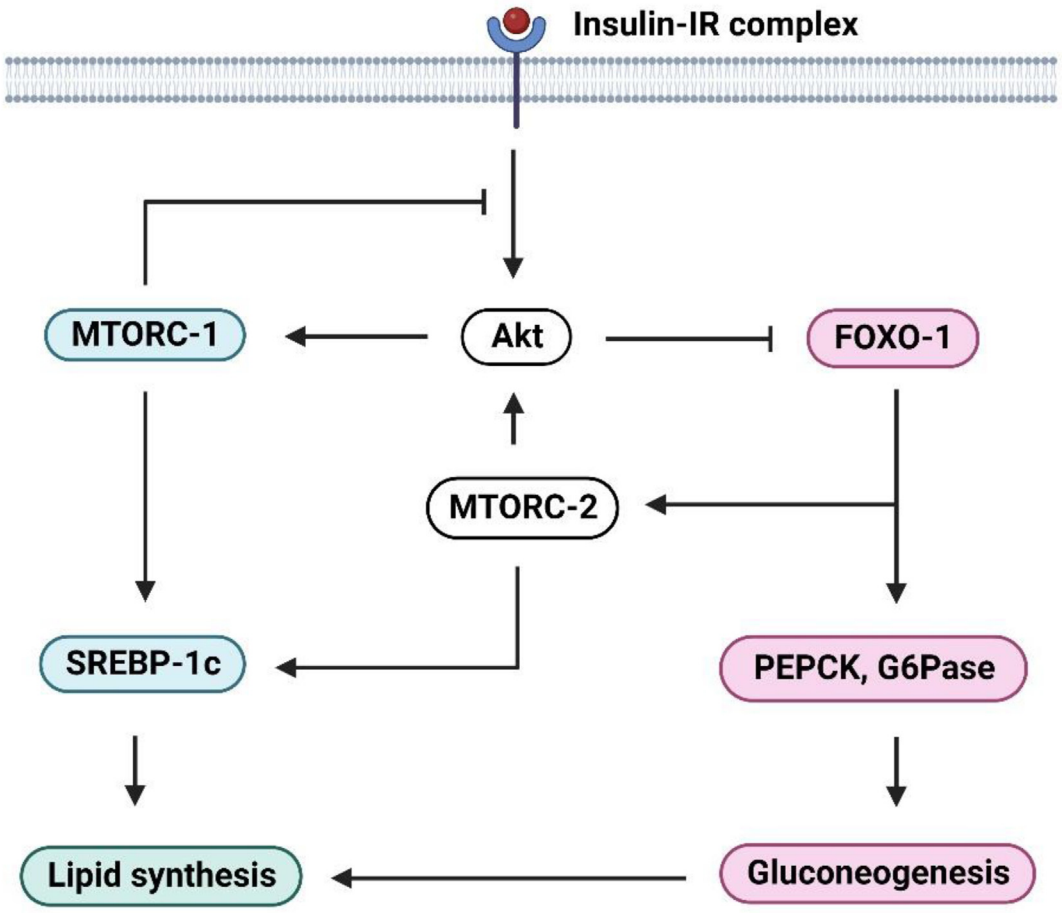

Figure 2. Previously reported lipogenic effect of Foxo-1 via MTORC -2 and suggested involvement of gluconeogenesis in lipid synthesis. The MTORC-2 pathway has inbuilt negative regulation loops while the gluconeogenesis pathway may cause uncontrolled lipogenesis through glucagon resistance as illustrated in Figure 4.

steatosis at least partly via Foxo-1 and MTORC-2 [20-21]. On the other hand, Foxo-1 also has anti-lipogenic activity, by inhibiting the nuclear localization of the transcription factor, carbohydrate response element binding protein (ChREBP) [22]. Moreover, MTORC-2, by activating akt [17], inhibits Foxo-1, such that lipogenesis dependent on Foxo-1 and MTORC-2 should be self-regulating (Figure 2). Similar negative feedback of MTORC-1 on akt through serine phosphorylation of IRS1/2 [23] may also partly explain the fact that in insulin-sensitive individuals, insulin-mediated lipogenesis is not excessive.

Ter Horst et al. [11] recently reported that fructose ingestion induced hepatic fatty acid synthesis in patients with NAFLD as well as in control subjects independently of insulin, through elevated expression of ChREBPβ. Thus, they concluded that hepatic lipid synthesis merely depends on the availability of lipogenic substrates in the liver, and that the HIR paradox does not exist. They suggested that the increased availability of lipogenic substrates in the liver may be due to (i) dietary intake of fructose and lipogenic amino acids (ii) muscle insulin resistance, causing greater availability of glucose in the liver, or (iii) increased adipose lipolytic activity, leading to increased free fatty acids in the liver, whose oxidation yields acetyl-CoA, which activates pyruvate carboxylase to promote gluconeogenesis. This study is important in providing a mechanism for excessive de novo lipogenesis under conditions of reduced insulin signaling, similarly to the studies suggesting the importance of Foxo-1 in lipogenesis. The suggestion that muscle insulin resistance can be a source of increased glucose availability in the liver would apply in individuals with (pre)diabetes, and it is known that diabetes promotes the pathogenesis of NAFLD [8]. On the other hand, it cannot explain the common scenario where NAFLD precedes (pre)diabetes [8]. Likewise, it is true that increased adipose lipolysis plays a role in increasing hepatic gluconeogenesis. However, NAFLD also occurs independently of obesity, including visceral obesity [24, 25]. Moreover, HIR often precedes adipose and muscle insulin resistance, as previously reviewed [26, 27]. For example, psychosocial stress, which induces hepatic steatosis via Foxo-1 [19,28], induces HIR prior to insulin resistance in muscle, adipose tissue, or brain [29].

3. Evidence that gluconeogenesis contributes to de novo lipid synthesis during HIR

Black women have a lower susceptibility than white women to fasting hyperglycemia, due to lower gluconeogenesis in the former, who also have lower susceptibility to developing hepatic steatosis [30]. In NAFLD patients, lipogenesis is highest in the fasting state and lowest after glucose ingestion [11]. This suggests that glucagon, whose concentration increases during fasting, promotes hepatic lipogenesis through gluconeogenesis in individuals with HIR. On the other hand, glucose ingestion suppresses lipogenesis in these individuals because it induces a surge in insulin secretion, which promotes somatostatin secretion by pancreatic delta cells, and both insulin and somatostatin suppress glucagon secretion [31]. This is consonant with the finding of Gar et al. [32] that there is a potential link between hepatic fat accumulation and insulin resistance via glucagon.

In an in vitro study, culturing hepatocytes under hyperglycemic conditions was found to induce steatosis, which was interestingly associated with the development of insulin resistance and upregulation of the gluconeogenic enzymes PEPCK and G6Pase [33]. On the other hand, hepatic silencing of the cytosolic isoform of PEPCK inhibits gluconeogenesis, de novo lipogenesis and dyslipidemia in db/db mice [34]. Thus,

HIR-induced gluconeogenesis should be an important player in excessive de novo lipogenesis even when lipogenic substrates such as glucose are supplied from extrahepatic sources. The lipogenic effect of Foxo-1 (Section 2) may thus be partly dependent on its upregulation of PEPCK and G6Pase, and resultant gluconeogenesis. The lipogenic effect of Foxo-1 via autophagy [18] can also be attributed to gluconeogenesis, since autophagy promotes gluconeogenesis by selectively degrading the circadian clock repressor, CRY1 [35]. Thus, as suggested in Figure 2, gluconeogenesis should be considered as an important contributor to Foxo-1-dependent lipogenesis, by mechanisms described in Sections 5-7.

4. Zonation of hepatic metabolism and fatty acid synthesis

Hepatocytes exist in three different zones of the hepatic acinus, namely the periportal, intermediate and pericentral zones, which exhibit differences in metabolism, such as high and low gluconeogenic activity in the periportal and pericentral zones, respectively [6, 36]. Berndt et al. [6] found that periportal hepatocytes exhibit higher fatty acid synthesis and very low-density lipoprotein (VLDL) secretion than pericentral hepatocytes. However, other studies reported contrary results, which is seemingly consistent with the fact that hepatic steatosis in human adults is mainly pericentral [36, 37]. Higher fatty acid oxidation and VLDL secretion in the periportal zone may prevent fat accumulation in this area despite its high fatty acid synthesis and uptake rates [6]. Regardless of the controversy regarding the zone of greater fatty acid synthesis, gluconeogenesis by the periportal hepatocytes may have a key role in fatty acid synthesis in both zones (Section 12).

5. The role of glycolysis in lipogenesis

As reviewed by Han et al. [38] and illustrated in Figure 3, the synthesis of fatty acids from glucose begins with the glycolytic pathway which converts glucose to pyruvate in the cytoplasm. Pyruvate is converted by the mitochondrial enzyme, pyruvate dehydrogenase (PDH) to acetyl-Coenzyme A (acetyl-CoA). Subsequently, citrate synthase (CS) catalyzes the reaction of acetyl-CoA with oxaloacetate to form citrate, which is translocated to the cytoplasm, where ATP-citrate lyase (ACLY) cleavages it back to acetyl-CoA and oxaloacetate. Acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN) then catalyze the synthesis of saturated fatty acids from acetyl-CoA. Palmitate, the longest fatty acid thus synthesized, can be converted by desaturation and/or elongation to palmitoleate, stearate and oleate.

Insulin signaling activates glucokinase (GCK), the first enzyme of the glycolytic pathway, besides upregulating fatty acid synthesis genes via SREBP-1c [38]. In insulin resistant individuals, glycolysis may instead be driven by fructose, fructose-1-phosphate and other sugar phosphates that activate glucokinase and ChREBP [11, 39].

6. Excessive gluconeogenesis promotes uncontrolled fatty acid synthesis through fructose synthesis and metabolism

Increased gluconeogenesis may induce hepatic hyperglycemia. Hepatic glucose is always higher than blood glucose, and when hepatic glucose increases, hepatocytes increase their consumption of the same, through increased activity of glucokinase [6, 40]. One of the pathways

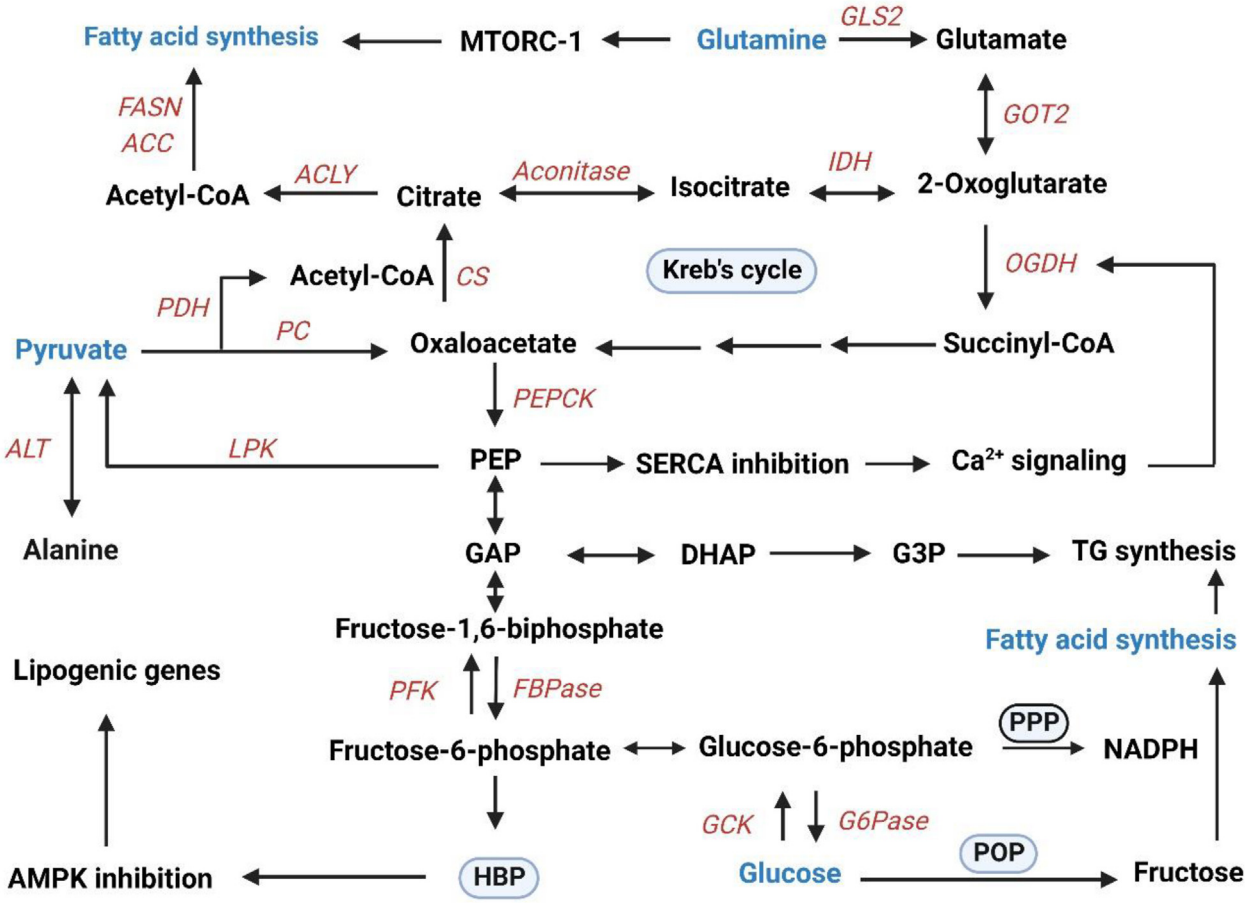

Figure 3. The roles and interactions of glycolysis, gluconeogenesis, polyol pathway (POP), glutamine anaplerosis, Kreb's cycle, hexosamine biosynthetic pathway (HBP) and pentose phosphate pathway (PPP) in hepatic lipid synthesis. ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ALT, alanine aminotransferase; CS, citrate synthase; FAS, fatty acid synthase; FBPase, fructose 1,6-biphosphatase; GCK, glucokinase; G6Pase, glucose-6-phosphatase; GLS 2, glutaminase 2; GOT 2, glutamate-oxaloacetate transaminase 2; IDH, isocitrate dehydrogenase; LPK, L-type pyruvate kinase; OGDH, 2-oxoglutarate dehydrogenase; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase.

involved in hepatic glucose consumption is glycolysis, which contributes to lipid synthesis (Section 5). Hyperglycemia also increases glucose flux through the polyol pathway (POP), which generates fructose (Figures 3 and 4) [41-42]. Fructose undergoes fructolysis, beginning with its fructokinase-catalysed phosphorylation to form fructose-1-phosphate (F1P), and enters the glycolytic pathway at the level of the triose phosphates, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) [41]. Glycolysis converts these triose phosphates to pyruvate, which is further metabolized to acetyl-CoA. Thus, fructose is readily converted via F1P to acetyl CoA and subsequently to fatty acids (Figure 4). Moreover, F1P activates glucokinase (GCK), which promotes the uptake and conversion of glucose to glucose-6-phosphate [39]. Glucose-6-phosphate activates ChREBPα, which upregulates the constitutively active ChREBPβ, which upregulates glycolytic genes such as liver-type pyruvate kinase (LPK) and lipogenic genes [11, 43].

7. Excessive gluconeogenesis promotes lipogenesis through uric acid synthesis, hexosamine biosynthetic pathway, and AMPK inhibition

The rapid conversion of fructose to fructose-1-phosphate causes a transient reduction in cellular ATP and an increase in AMP, which promotes degradation of the latter to form uric acid [44, 45]. Rabbits on a high fat diet (HFD) develop NAFLD accompanied by hepatic uric acid accumulation [46]. This is consistent with HFD-mediated induction of HIR, and HIR-induced gluconeogenesis and fructose synthesis. Accordingly, hyperuricemia is a risk factor for NAFLD [47]. Interestingly, obese female mice with hepatic steatosis and glucose intolerance were recently found to have hepatic hyperuricemia even in the absence of systemic hyperuricemia [48]. Uric acid-dependent development of hepatic steatosis involves its activation of aldose reductase and fructokinase (FK) (Figure 4) [49, 50]. Aldose reductase initiates the polyol pathway (POP), and FK converts fructose to F1P, thereby initiating fructose metabolism and associated increase in glycolysis and fatty acid synthesis [49, 50]. In addition, uric acid activates NADPH oxidase, which induces ER stress [44].

ER stress promotes insulin resistance and associated gluconeogenesis [14]. It also contributes in various ways to the activation of lipogenic transcription factors such as SREBP-1c, ChREBP, and liver X-receptor (LXR) (Figure 4). For example, ER stress triggers the unfolded protein response (UPR) [14]. The ER stress-UPR nexus upregulate glutamine: fructose-6-phosphate aminotransferase 1 (GFAT1), and O-glucosyl aminotransferase (OGT), key enzymes of the hexosamine biosynthetic pathway (HBP), which causes the O-GlucNAcylation of proteins [51, 52, 53]. The gluconeogenic pathway intermediate, fructose-6-phosphate, is a substrate of GFAT1 [51]. HBP also induces ER stress [54]. O-GlucNAcylation activates ChREBP and liver X receptor (LXR) [52, 55]. Global protein O-GlucNAcylation markedly inhibits AMP-activated protein kinase (AMPK), leading to activation of the fatty acid synthesis enzymes ACC and FASN as well as ChREBP, SREBP-1c, and LXR [54, 56, 57, 58]. LXR upregulates SREBP-1c and CD 36 [59]. CD 36 forms a complex with insig2 to disrupt the latter's inhibition of SREBP-1c [60], and is

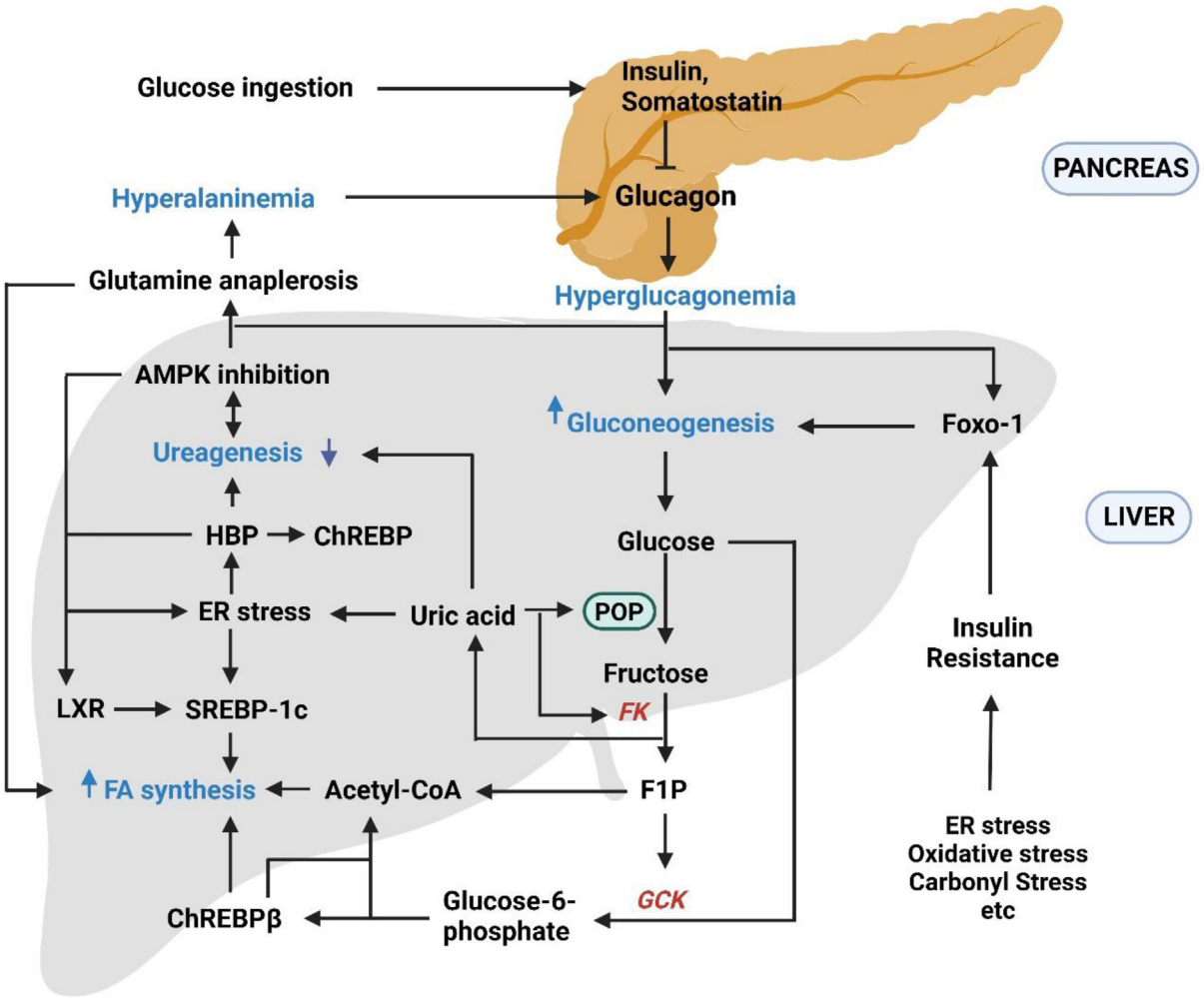

Figure 4. Proposed etiology of glucagon resistance, characterized by increased gluconeogenesis, decreased urea synthesis, hyperalaninemia, hyperglucagonemia, and increased fatty acid synthesis. FA, fatty acid; HBP, hexosamine biosynthetic pathway; LXR, liver X receptor; POP, polyol pathway.

upregulated in hepatocytes exposed to hyperglycemia [33]. Hence, HBP promotes NAFLD and steatosis in hepatocytes [53, 54, 55].

O-GlucNAcylation does not directly affect AMPK activity, or even increases it, hence the reason for the inhibition of this kinase during global O-GlucNAcylation in hepatocytes is not clear [55]. A possible explanation is that urea synthesis plays a significant role in hepatic AMPK activation through activity of argininosuccinate synthetase [61], but the urea cycle enzyme, carbamoyl phosphate synthetase 1 (CPS-1) is readily O-GlucNAcylated, leading to its inhibition, and resultant inhibition of the urea cycle [62]. Since AMPK in turn upregulates the expression of CPS-1 and another urea cycle enzyme, ornithine transcarbamoylase [63], there is a vicious cycle between AMPK inhibition and inhibition of ureagenesis (Figure 4).

8. Glucagon resistance exacerbates gluconeogenesis-associated lipogenesis

Ordinarily, glucagon signaling promotes gluconeogenesis, amino acid catabolism, urea synthesis, and fatty acid oxidation, while inhibiting fatty acid synthesis, thereby preventing hepatic steatosis [64]. Nevertheless, glucagon signaling activates liver kinase B (LKB), which activates AMPK [64], which prevents excessive gluconeogenesis by antagonizing cAMP response element-binding protein (CREB)-induced expression of PEPCK and glucose-6-phosphatase [65]. In NAFLD, the phenomenon of glucagon resistance occurs, characterized by decreased urea synthesis, hyper aminoacidemia (including hyperalaninemia), hyperglucagonemia, enhanced lipogenesis, and increased gluconeogenesis [64, 66, 67, 68, 69, 70].

The etiology of glucagon resistance is not well-understood [70]. However, as already described in Section 7, inhibition of urea synthesis at least partly involves O-GlucNAcylation of CPS-1, due to increased HBP activity. Additionally, uric acid (and xanthine) inhibits N-acetylglutamate synthase, whose product is an obligatory activator of CPS-1 [71]. Likewise, argininosuccinate synthetase is downregulated by uric acid via activation of hypoxia inducible factor 1 alpha [72].

As shown in Figure 4, AMPK inhibition may be pivotal in glucagon resistance, because, apart from reducing ureagenesis, it promotes gluconeogenesis and lipogenesis [73]. In addition, AMPK promotes the catabolism of branched chain amino acids [74], hence its inhibition can cause hyperaminoacidemia.

The main cause of hyperglucagonemia in glucagon resistance is hyperalaninemia, since alanine induces glucagon secretion by pancreatic alpha cells (Figure 4) [32, 66].

Hyperalaninemia was suggested to be caused by increased glutamine anaplerosis and resultant preferential gluconeogenesis from glutamine rather than from alanine [75].

Glutamine anaplerosis can be caused by AMPK inhibition and other factors associated with excessive gluconeogenesis such as ER stress and urea pathway inhibition (Figure 4) (Section 9).

Thus, four of the known features of glucagon resistance, namely increased gluconeogenesis, decreased urea synthesis, hyperalaninemia and hyperglucagonemia, together with glutamine anaplerosis, can be considered to be part of a vicious cycle that perpetuates fatty acid synthesis (Figure 4).

9. Excessive gluconeogenesis promotes glutamine anaplerosis and vice versa

In hepatocytes, glutamine anaplerosis involves glutaminase 2-catalyzed glutaminolysis to produce glutamate and ammonia, followed by glutamate-oxaloacetate transaminase 2 (GOT2)-catalyzed conversion of glutamate to the Kreb's cycle intermediate, 2-oxoglutarate (Figure 3) [76]. Gluconeogenesis may promote glutamine anaplerosis via uric acid, ER stress, HBP, decreased urea synthesis and AMPK inhibition (Figure 4). AMPK inhibition promotes the activation of MTORC-1 [77]. MTORC-1 activates myc, which upregulates the glutamine transporter SLC1A5, thereby increasing glutamine uptake by the hepatocytes [78]. Reduced urea synthesis not only inhibits AMPK but also increases the intracellular ammonia, and the latter activates glutaminase 2 [79]. ER stress, which can be induced by uric acid, HBP, and AMPK inhibition causes calcium efflux from the ER and its influx into mitochondria [54, 80, 81]. The PEPCK product, PEP, also inhibits the calcium pump SERCA to increase mitochondrial calcium [76, 82]. Mitochondrial calcium promotes glutamine anaplerosis by activating 2-oxoglutarate dehydrogenase (OGDH), which converts 2-oxoglutarate to succinyl-CoA, thus favouring the GOT2-catalysed conversion of glutamate to 2-oxoglutarate rather than the reverse reaction (Figure 3) [75, 83]. Succinyl-CoA may further activate glutaminase by succinylation [84]. PEPCK contributes to glutamine anaplerosis not only through PEP-induced calcium signaling, but also because its conversion of oxaloacetate to PEP is cataplerotic, necessitating oxaloacetate replenishment through anaplerosis [85].

PEP produced subsequently to glutamine anaplerosis may be converted by LPK to pyruvate, and alanine aminotransferase (ALT) catalyses the reversible conversion of pyruvate to alanine (Figure 3). Hence, glutamine anaplerosis, by increasing the concentration of pyruvate, may promote alanine synthesis, resulting in hyperalaninemia. Accordingly, infusion of L-glutamine to the portal vein of type 2 diabetic rats was found to increase L-alanine production without much change in gluconeogenesis [86]. In the kidney, such conversion of glutamate to alanine is well-known [87]. Thus, glutamine anaplerosis promotes hyperalaninemia not just by reduced alanine catabolism [75], but also by increased alanine synthesis from pyruvate. Hyperalaninemia, promotes hyperglucagonemia, which in turn promotes glutamine anaplerosis (Figure 4), because glucagon signaling activates the endoplasmic reticulum's InsP3R1 receptors to release ER calcium [83], besides activating PEPCK.

10. Glutamine anaplerosis promotes lipid synthesis through both oxidative metabolism and reductive carboxylation of 2-oxoglutarate

As described in Section 9, the oxidative metabolism of 2-oxoglurate leads to formation of alanine via pyruvate. The latter can alternatively be converted by PDH to acetyl-CoA for fatty acid synthesis (Figure 3). Increased mitochondrial calcium, which activates 2-oxoglutarate dehydrogenase, also activates PDH [88].

Most cell types including human hepatocytes and hepatocyte-like cells also metabolize glutamine to produce fatty acids through the reductive carboxylation of 2-oxoglutarate to produce isocitrate, which is then converted via citrate to acetyl-CoA (Figure 3) [82, 89, 90]. Such glutamine metabolism involving reductive carboxylation of 2-oxoglutarate is a major contributor to hepatic fatty acid synthesis even in healthy individuals [91].

Reductive carboxylation occurs under conditions of reductive stress, where the NAD+: NADH ratio or NADP+: NADPH ratio in a cellular compartment declines to the extent that it affects metabolism [92]. Oxidative metabolism of 2-oxoglutarate to oxaloacetate, which is enhanced during elevated glutamine anaplerosis, contributes to the conversion of NAD+ to NADH. Moreover, increased flux through α−ketoglutarate dehydrogenase is a major source of hepatic mitochondrial reactive oxygen species (ROS) [93], which damage DNA, and thus stimulate the DNA repair enzyme, poly ADP ribose polymerase-1 (PARP-1) [94]. PARP-1 catalyses PARylation of proteins, a reaction that consumes NAD+ by transferring ADP-ribose units from the latter to proteins [95, 96]. Protein PARylation was found to be associated with lower NAD + levels and induction of steatosis [97].

The mitochondrial electron transport chain is pivotal for maintaining the mitochondrial NAD+: NADH ratio because its component, complex 1, oxidizes NADH, and transfers the electrons to oxygen via complexes 3 and 4 [98]. Inhibition of any of these complexes inhibits NADH oxidation, thereby promoting reductive stress. Mitochondrial calcium inhibits complex 1 [99]. ROS-dependent peroxidation of cardiolipin also induces

reductive stress, since this mitochondrial membrane phospholipid is required for the assembly of ETC complexes 1, 3, and 4 into supramolecular complexes (respirasomes), which facilitate efficient electron transfer between the complexes [98, 100]. Additionally, hyperglucagonemia suppresses complexes 3 and 4 via Foxo-1-mediated reduction in heme production [101].

During reductive stress, the inner mitochondrial membrane enzyme, nicotinamide nucleotide transhydrogenase (NNT) catalyses the thermodynamically favourable coupling of NADH oxidation to the reduction of NADP+ to form NADPH, thus establishing a much higher mitochondrial NADPH/NADP+ than NADH/NAD+ ratio [102]. In the Kreb's cycle, isocitrate dehydrogenase 2 catalyzes the oxidative decarboxylation of isocitrate to form 2-oxoglutarate, which is coupled to the reduction of NADP+ to NADPH. However, the high NADPH/NADP+ ratio generated by NNT makes this reaction unfavourable, and promotes the otherwise thermodynamically unfavourable reverse reaction, namely the reductive carboxylation of 2-oxoglutarate to isocitrate, which is then converted by aconitase to citrate [102].

Reductive stress and associated reductive carboxylation are likely to be oscillatory rather than continuous. This is because a period of reductive carboxylation should raise the mitochondrial NADP+: NADPH ratio, and by extension the NAD+: NADH ratio [103]. Another NADPH-dependent process that may play a role in ameliorating mitochondrial reductive stress is mitochondrial fatty acid synthesis (MFAS), which is involved in the de novo synthesis of lipoic acid (LA) via octanoic acid, and is essential for cellular respiration and mitochondrial biogenesis [104, 105]. Besides oxidizing NADPH, MFAS generates 3-hydroxymyristoyl-ACP, a component of mammalian mitochondrial complex I [106], thereby enhancing ETC complex assembly and NADH oxidation [105]. Such periodic relief from reductive stress is necessary for the continued operation of NAD+ -dependent reactions of the Krebs cycle. It enables the conversion of 2-oxo-glutarate via oxaloacetate to PEP, which is an intermediate in glucose, alanine and fatty acid synthesis.

11. Gluconeogenic pathway activity promotes lipogenesis even independently of glucose production

Montal et al. [82] reported that colon cancer cells metabolize glutamine in a PEPCK-dependent manner to promote the pentose phosphate pathway (PPP), nucleotide synthesis and fatty acid synthesis, but without glucose production. Hepatocyte-like cells exposed to a mixture of pyruvate, lactate and octanoate were found to develop steatosis associated with gluconeogenic pathway activity but no glucose production [89]. In the former study, glutamine anaplerosis can lead to fatty acid synthesis through reductive or oxidative metabolism of 2-oxoglutarate, and the oxidative metabolism also supplies PEP for the gluconeogenic pathway (Figure 3). In the latter study, pyruvate acts as a precursor for both fatty acid synthesis and gluconeogenesis (Figure 3), and lactate acts a precursor of pyruvate.

Gluconeogenic pathway intermediates can promote lipogenesis in various ways. For example, glucose-6-phosphate is a substrate for the PPP, which supplies NADPH for lipogenesis [82]. This sugar phosphate activates ChREBP [11, 107]. Dihydroxyacetone phosphate activates MTORC-1, which activates SREBP-1c [108]. MTORC-1-SREBP1 signaling upregulates glucose-6-phosphate dehydrogenase, the first enzyme of PPP [109]. Fructose-6-phosphate is a substrate of the hexosamine biosynthetic pathway (HBP), which induces activation of ChREBP by O-GlucNAcylation [52]. HBP-induced AMPK inhibition activates multiple lipogenic factors and promotes glutamine anaplerosis (Section 7 and Figure 4). Ammonia produced during glutamine anaplerosis activates SREBP-1c by inducing the dissociation of SCAP from Insig [110]. Glutamine anaplerosis induces mitochondrial oxidative stress, which impairs ETC activity (Section 10). Reduced ATP levels as a result of ETC inhibition promotes purine nucleotide degradation and the synthesis of uric acid [111], which upregulates lipogenic genes as depicted in Figure 4. Thus, heightened gluconeogenic pathway activity during HIR can promote lipid synthesis independently of glucose production.

12. Consolidated pathways of gluconeogenesis-associated hepatic lipid synthesis

The zonation of hepatic metabolism affects pathways related to lipid synthesis in hepatocytes. For example, periportal hepatocytes (PPHs) take up and catabolize glutamine but not glutamate, while pericentral hepatocytes (PCHs) take up glutamate and ammonia to synthesize glutamine [89, 112, 113]. With this in mind, the mechanisms of gluconeogenesis-dependent lipid synthesis (Sections 5-11) can be summarized as illustrated in Figures 5 and 6 for PPHs and PCHs, respectively.

In PPHs, inhibition of insulin signaling activates Foxo-1, which activates PEPCK (Figure 5). PEPCK catalyses the cataplerotic conversion of oxaloacetate to 2-phosphoenol pyruvate (PEP), which is metabolized in the gluconeogenic pathway to produce glucose. PEPCK activity and increased PEP concentration promote glutamine anaplerosis to establish a vicious cycle for PEP production (Section 9). When flux through PEPCK and the rest of the gluconeogenic pathway is high, intermediates such as dihydroxyacetone phosphate, fructose-6-phosphate and glucose-6-phosphate upregulate glycolytic and lipogenic genes via MTORC-1, ChREBP the HBP (Section 11). The glycolytic enzyme LPK converts PEP to pyruvate, some of which is converted by ALT to alanine, which stimulates glucagon secretion by pancreatic alpha cells. Glucagon signaling promotes glutamine anaplerosis through PEPCK upregulation and activation of the InsP3R1 receptor (Section 9). Glutamine anaplerosis-derived pyruvate is also metabolized via acetyl-CoA to citrate in the mitochondria. Citrate is transported to the cytoplasm and cleaved back to oxaloacetate and acetyl-CoA, the latter being the substrate for fatty acid synthesis.

Glutamine anaplerosis causes mitochondrial oxidative stress and reductive stress (Section 10). Reductive stress promotes fatty acid synthesis via the reductive carboxylation of 2-oxoglutarate. A major cause of reductive stress is impairment of the mitochondrial ETC, which inhibits the oxidation of NADH to NAD+. ETC inhibition also reduces ATP production. Low ATP due to ETC inhibition promotes purine degradation and uric acid synthesis [111]. Uric acid (i) induces oxidative stress and associated ER stress, which promotes glutamine anaplerosis (ii) activates aldose reductase to promote the polyol pathway (POP) which converts glucose to fructose and (iii) activates fructokinase, whose activity initiates fructose metabolism to triose phosphate glycolytic intermediates and lowers cellular ATP to increase uric acid synthesis, and (iv) promotes the HBP, which inhibits the urea cycle, thereby causing AMPK inhibition, which promotes glutamine anaplerosis, and induces lipogenic enzymes (Sections 7-8).

When extracellular glucose increases beyond a certain threshold (which is lower for PCHs than PPHs), hepatocytes, especially PPHs greatly increase glucose uptake and glycolysis [6]. This is facilitated by fructose-1-phosphate, which activates glucokinase, which promotes glucose uptake and its conversion to glucose-6-phosphate. Thus, in hyperglycemia, hepatocytes exhibit high glycolytic and gluconeogenic pathway fluxes, consistent with the report that culturing hepatocytes in hyperglycemic conditions promotes both steatosis and gluconeogenesis [33]. Just as reductive stress and associated reductive glutamate carboxylation are expected to be oscillatory (Section 10), the glycolytic and gluconeogenic fluxes should occur in alternating periodic cycles. Gluconeogenesis is expected to coincide with periods of oxidative metabolism of 2-oxoglutarate when mitochondrial ATP synthesis is high, while glycolysis coincides with peak periods of reductive stress when ATP is lower.

As shown in Figure 6, pericentral hepatocytes (PCH) take up glucose, uric acid, glutamate and ammonia released from their periportal counterparts (PPH) through GLUT2, GLUT9, excitatory amino acid transporter 2 (EAAT2) and Rhesus family B glycoprotein (RhBG), respectively [113, 114, 115]. These hepatocytes have a high glycolytic

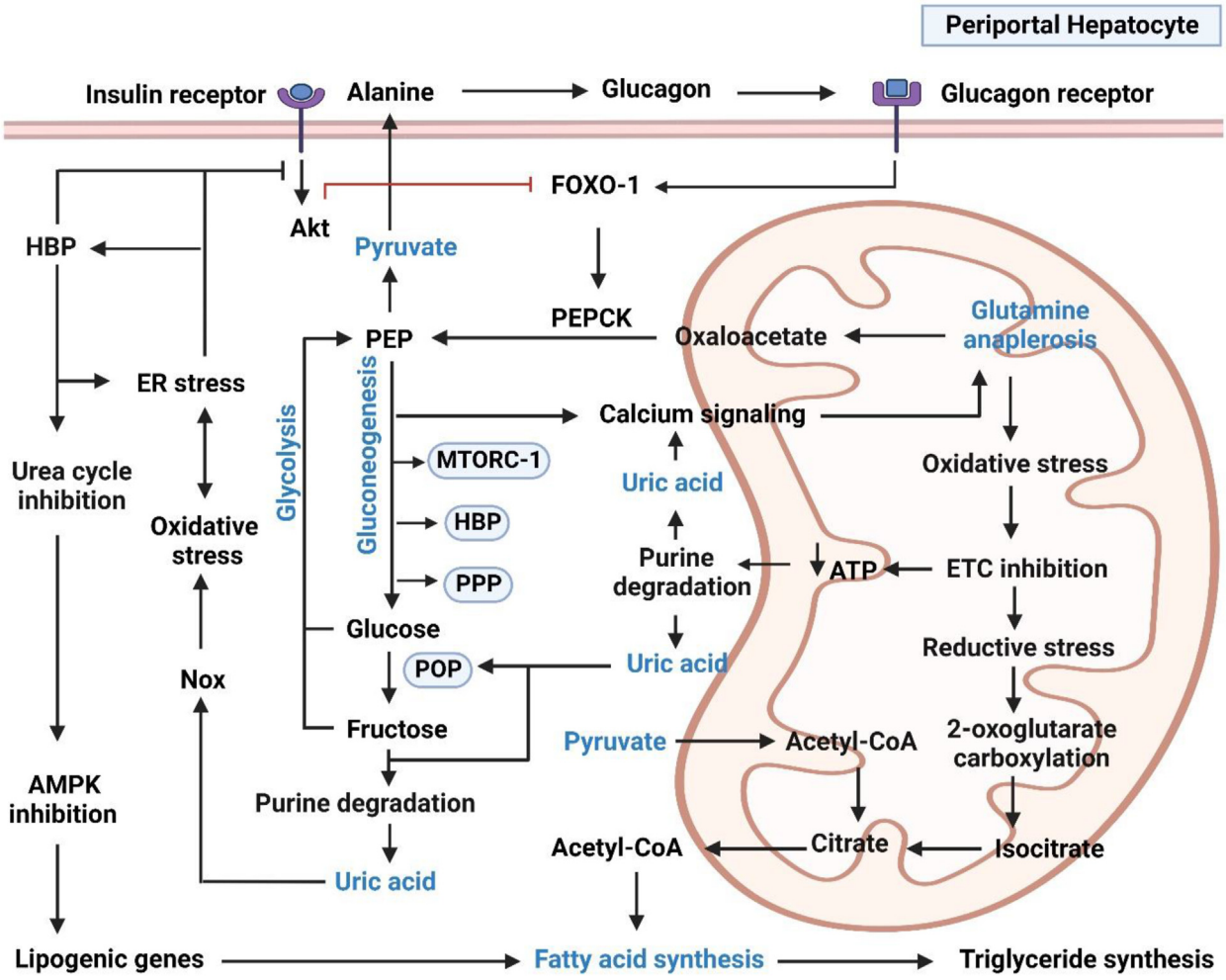

Figure 5. A unified presentation of the mechanisms for gluconeogenesis-associated fatty acid synthesis by periportal hepatocytes.

activity, which plays a big role in their synthesis of fatty acids [6]. The imported uric acid promotes glycolysis and fatty acid synthesis by mechanisms already explained, such as inducing fructose synthesis and metabolism. In both PPHs and PCHs, fructose, glucose and the triose phosphate gluconeogenesis/glycolysis intermediates undergo the Maillard reaction, leading to formation of advanced glycation end products such as carboxymethyl lysine (CML). CML interacts with SCAP to activate SREBP-1c [116].

The glutamate and ammonia imported by PCHs are converted by glutamine synthetase to glutamine [115]. Glutamine and ammonia activate MTORC-1 [117] and SREBP-1c, respectively [110]. Additionally, glutamate uptake promotes the activation of NF-kB, which upregulates glutamate-oxaloacetate transaminase (GOT) [118]. GOT converts glutamate and oxaloacetate to 2-oxoglutarate and aspartate, respectively. 2-Oxoglutarate can be transported through its mitochondrial carrier into the mitochondrion, where its oxidative metabolism in the Kreb's cycle leads to formation of oxaloacetate via malate. Some malate is transported to the cytoplasm where it is converted via oxaloacetate to pyruvate, a precursor of both fatty acid and alanine synthesis. Accordingly, glutamate infusion into the portal vein was found to lead to rapid alanine synthesis by PCHs [119]. Fatty acid synthesis from imported glutamate also occurs by the reductive carboxylation of 2-oxoglutarate [120]. There are cytoplasmic and mitochondrial isoforms of GOT, isocitrate dehydrogenase and aconitase. Therefore, citrate formation through reductive carboxylation can occur in both cytoplasm and mitochondria [76, 121].

13. Excessive gluconeogenesis successively induces NAFLD and blood glucose dysregulation

Non-alcoholic fatty liver disease (NAFLD) often precedes blood glucose dysregulation and is an independent risk factor for impaired fasting glucose and type 2 diabetes, an association which is not well understood [8]. From the foregoing discussion, it can be concluded that gluconeogenic pathway activity can promote lipid synthesis even without glucose production (Section 11). Moreover, when gluconeogenesis causes excessive glucose production, excess glucose is channelled to lipogenesis (Sections 6, 12), thus inducing NAFLD without necessarily dysregulating blood glucose. However, with sustained gluconeogenesis and NAFLD, this system gets overwhelmed, allowing more glucose delivery to the blood. This is consistent with the fact that increasing liver fat content is associated with the dysregulation of blood glucose [122, 123]. The activating transcription factor 3 (ATF3), whose expression increases with steatosis, and is a predictor of diabetes in people with NAFLD, promotes both gluconeogenesis and lipid synthesis [124]. However, it represses the transcription of the hepatocyte glucose sensor, glucokinase, thus reducing hepatic glucose consumption [125]. Additionally, the hyperuricemia associated with excessive gluconeogenesis induces pancreatic beta cell dysfunction, and may with time cause relative insulin insufficiency, which promotes hyperglucagonemia and diabetes [31, 126]. The increased circulating glucose in diabetes further promotes HIR, gluconeogenesis and lipid synthesis, thereby accentuating NAFLD [33, 41]. Such a view that gluconeogenesis contributes to both NAFLD and

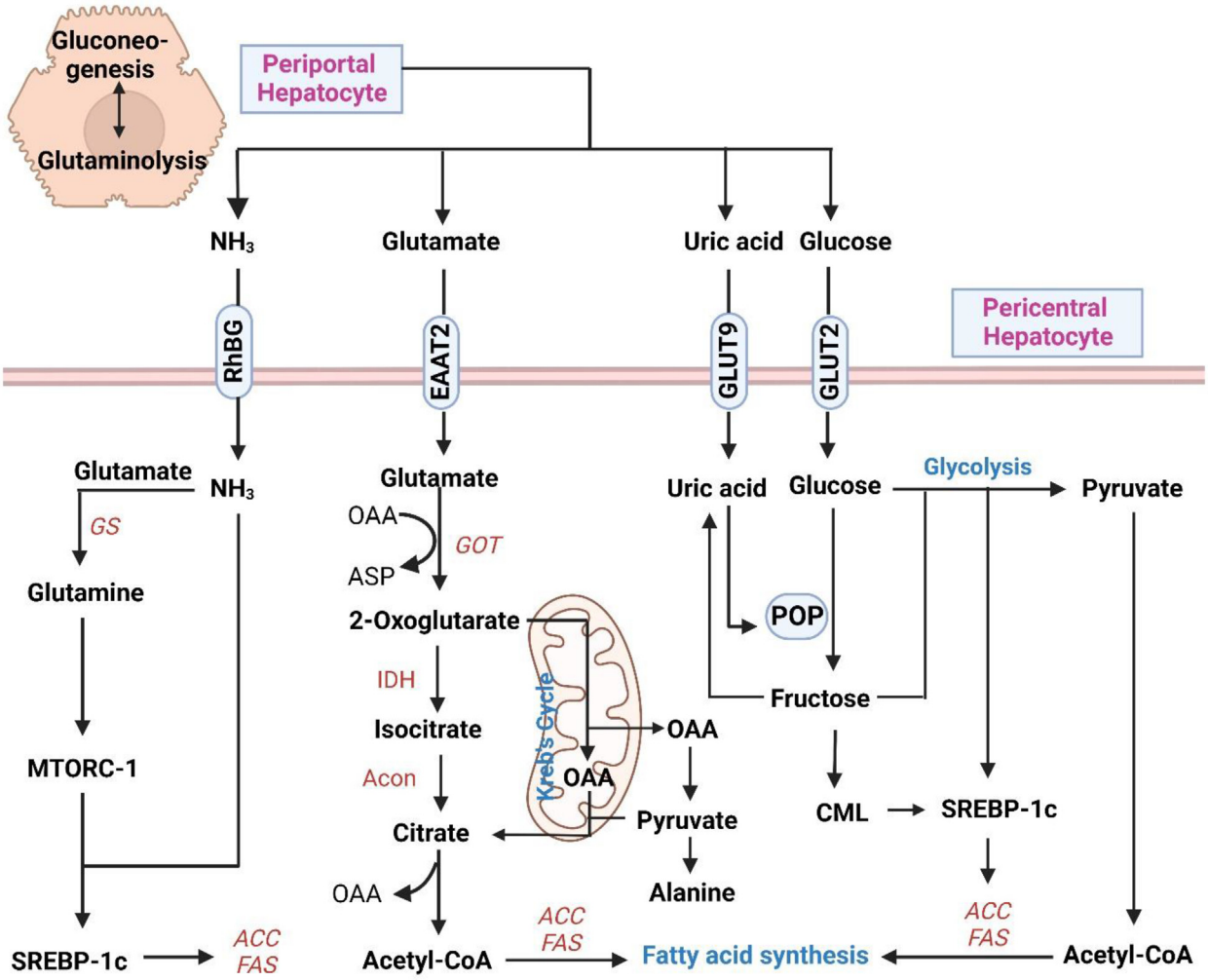

Figure 6. A unified presentation of the mechanisms of gluconeogenesis-associated fatty acid synthesis by pericentral hepatocytes. Although these hepatocytes have low gluconeogenic activity, their fatty acid synthesis can be driven by gluconeogenesis in periportal hepatocytes. CML, carboxymethyl lysine.

(pre)diabetes rationalizes the fact that various antidiabetic drugs ameliorate NAFLD [127].

Although type 1 diabetes also exhibits increased hepatic gluconeogenesis, hyperglucagonemia and hyperglycemia, it is not a risk factor for NAFLD [128]. This can be attributed to the absence of glucagon resistance in type 1 diabetes, as manifested by increased hepatic urea synthesis efficiency [129]. In type 1 diabetes, hyperglucagonemia and associated hyperglycemia occur because of reduced insulin secretion. Notably, hyperinsulinemia, a characteristic of type 2 but not type 1 diabetes, causes reduced plasma adiponectin [130]. On the other hand, patients with type 1 diabetes have increased plasma adiponectin [131, 132]. Adiponectin signaling in hepatocytes activates AMPK and improves insulin sensitivity [133]. AMPK activation should inhibit all the components of glucagon resistance including lipogenesis (Figure 4). AMPK activates endothelial nitric oxide synthase, which produces nitric oxide, which inhibits xanthine oxidase [134]. Hence, type 1 diabetes is also associated with reduced uric acid synthesis [135].

14. Excessive gluconeogenesis drives the progression of NAFLD

NAFLD is a continuum of conditions including simple non-alcoholic steatosis (NAS) and steatosis with inflammation (non-alcoholic steatohepatitis, NASH); and NAS and NASH can occur with or without fibrosis [136, 137, 138]. Patients with NASH and/or fibrosis are more likely to progress to life-threatening conditions such as cirrhosis and hepatocellular carcinoma [136, 137]. The mechanisms of progression from NAS to NASH and fibrosis are not well understood, although it is widely explained by the 'two-hit theory,' whereby certain factors deliver the first hit that induces steatosis, and other factors or combination of factors deliver the second hit that causes conversion of steatosis to NASH and fibrosis [138]. Thus, HIR-induced gluconeogenesis can be considered as a major factor delivering the first hit since it causes steatosis as already explained. Moreover, sustained or severe gluconeogenesis can be considered to deliver the second hit through increased hepatocyte fat content, blood glucose dysregulation, hyperinsulinemia and hypoadiponectinemia as explained hereafter (Figure 7).

NASH is characterized by increased death of hepatocytes, which induces inflammation by promoting activation and recruitment of leukocytes such as macrophages and neutrophils [139]. Sheng et al. [140] reported that the pericentral hepatocytes which readily accumulate lipids are more prone to cell death and expression of pro-inflammatory cytokines, and that their susceptibility to death increases with increasing intracellular lipid content. Thus, severe or prolonged HIR and gluconeogenesis are likely to drive excessive hepatocyte fat accumulation, leading to hepatocyte death and NASH.

Among patients with NAFLD, more NASH cases occur in (pre)diabetes than normoglycemia, but the severity of NASH correlates more with hyperinsulinemia than hyperglycemia [141]. The increased cases of NASH in prediabetes as compared to normoglycemia is consistent with the fact that the degree of steatosis is also higher in prediabetes [122,

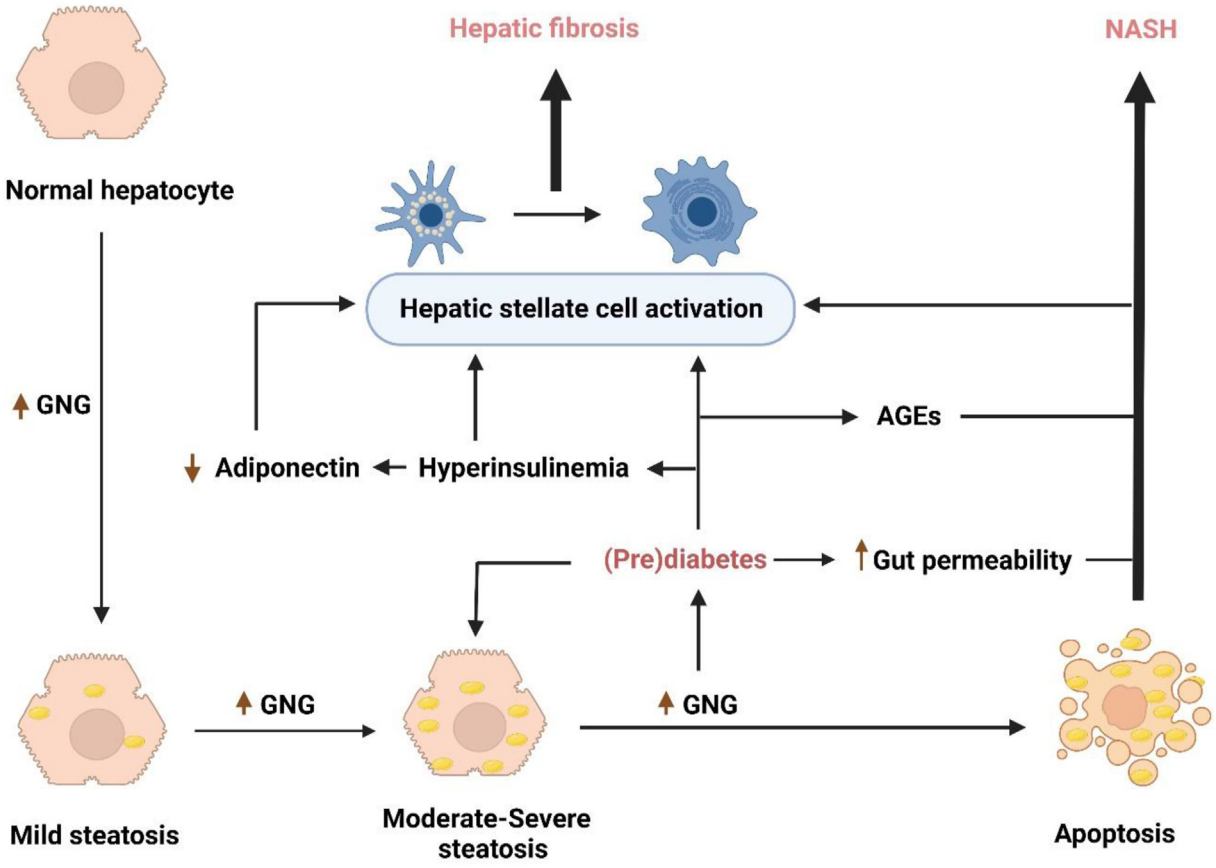

Figure 7. Proposed role of HIR-induced gluconeogenesis on the progression of NAFLD from simple steatosis to NASH and fibrosis. HSC, hepatic stellate cell. AGEs, advanced glycation end products. NASH, non-alcoholic steatohepatitis; GNG, gluconeogenesis.

123]. The relationship between hyperinsulinemia and NASH severity may be due to the association between hyperinsulinemia and hypoadiponectinemia [130], since the latter differs significantly between NAS and NASH, and is associated with increased inflammation [142]. As discussed in section 8, HIR-induced excessive gluconeogenesis can cause glucagon resistance, which is associated with hyperglucagonemia. Glucagon induces insulin secretion and hyperinsulinemia [31]. Hence, glucagon resistance may be a major contributor to hyperinsulinemia and hypoadiponectinemia. Blood glucose dysregulation also promotes hyperinsulinemia [143].

Fibrosis occurs when hepatic stellate cells (HSCs), which are normally quiescent, become activated to proliferate and produce excessive extracellular matrix [144, 145]. Fibrosis cases are higher in (pre)diabetes than normoglycemia and the severity of fibrosis is affected by blood glucose level [144]. This relationship exists because high glucose activates HSCs [145]. Adiponectin inhibits HSC activation [146], and the hyperinsulinemia that promotes hypoadiponectinemia directly promotes HSC activation [147]. Hepatocyte apoptosis also activates HSCs, hence fibrosis is more common in NASH than NAS [148].

Advanced glycation end products (AGES) contribute to the development of NASH and fibrosis [138]. The rate of formation of AGES depends on the concentrations of sugars [138]. Thus, excessive gluconeogenesis may promote fibrosis through the formation of AGES in the liver. Increased intestinal barrier permeability, which can be induced by blood glucose dysregulation, promotes the progression of NAFLD, through delivery of gut-derived harmful factors such as endotoxin to the liver [149, 150]. Thus, excessive gluconeogenesis can promote NASH through disruption of the gut barrier.

High fat diets or high fat-high sucrose diets also promote the progression of NAFLD [151, 152]. These diets promote HIR [153, 154], hence their effects on NAFLD progression may be mainly mediated by gluconeogenesis. Thus, it is likely that many of the factors that deliver the 'second hit' in NAFLD progression involve increased gluconeogenesis.

15. Conclusion

Excessive hepatic gluconeogenesis and/or gluconeogenic pathway activity promotes excessive lipid synthesis in insulin resistant hepatocytes, and is therefore a cause of the hepatic insulin resistance paradox. Hence, gluconeogenesis is an important factor in the development of diabetes, NAFLD, and dyslipidemia as consequences of hepatic insulin resistance (HIR). Furthermore, gluconeogenesis is involved in the progression of NAFLD from simple steatosis to NASH and fibrosis, that increase the risk for cirrhosis and hepatocellular carcinoma. Hence lifestyle, dietary, nutraceutical and pharmacological strategies to reduce HIR and hepatic gluconeogenesis should be targeted for the prevention and management of these diseases.

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