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REVIEW

Responses to Hypoxia: How Fructose Metabolism and Hypoxia-Inducible Factor-1a Pathways Converge in Health and Disease

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Abstract

Purpose of Review Oxygen is critical for the high output of energy (adenosine triphosphate) generated by oxidative phosphorylation in the mitochondria, and when oxygen delivery is impaired due to systemic hypoxia, impaired or reduced delivery of red blood cells, or from local ischemia, survival processes are activated.

Recent Findings One major mechanism is the activation of hypoxia-inducible factors (HIFs) that act to reduce oxygen needs by blocking mitochondrial function and stimulating glucose uptake and glycolysis while also stimulating red blood cell production and local angiogenesis. Recently, endogenous fructose production with uric acid generation has also been shown to occur in hypoxic and ischemic tissues where it also appears to drive the same functions, and indeed, there is evidence that many of hypoxia-inducible factors effects may be mediated by the stimulation of fructose production and metabolism. Unfortunately, while being acutely protective, these same systems in overdrive lead to chronic inflammation and disease and may also be involved in the development of metabolic syndrome and related disease. The benefit of SGLT2 inhibitors may act in part by reducing the delivery of glucose with the stimulation of fructose formation, thereby allowing a conversion from the glycolytic metabolism to one involving mitochondrial metabolism.

Summary The use of hypoxia-inducible factor stabilizers is expected to aid the treatment of anemia but, in the long-term, could potentially lead to worsening cardiovascular and metabolic outcomes. We suggest more studies are needed on the use of these agents.

Keywords Hypoxia-inducible factor · Fructose · Inflammation · Energy metabolism · Signaling pathways · Therapeutics

Introduction

Oxygen is an essential component for aerobic metabolic processes, which is required for maintaining life. One of the major roles of oxygen is in the production of energy (adenosine triphosphate, or ATP) by the mitochondria. Indeed, the vast majority of ATP produced in the body results from oxidative phosphorylation.

One of the greatest risks to organisms is hypoxia, a state in which oxygen levels at the tissue level are not adequate to maintain homeostasis [1]. Hypoxia can occur because of insufficient oxygen delivery to the tissues and/or low oxygen content in the blood, and it is a critical hallmark for many diseases.

HIFs and Survival from Hypoxia

To protect against hypoxia, the host has developed an orchestrated survival response that are mediated by hypoxia-inducible factors (HIF) (Table 1). HIFs are transcription factors that consist of a heterodimeric basic helix loop structure that has both

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Table 1 Short- and long-term effects of hypoxia-inducible factor (HIF) on different organs and systems in the body

	Why is HIF helpful in the acute ischemic state?	How does HIF and activation of fructose metabolism cause harm in the long term?
Main actions	• Increases oxygen availability • Promotes erythropoiesis and angiogenesis • Activates genes involved in glucose transport and metabolism • Affects glucose and lipid metabolism by binding to HRE sequence	• Promote lactate acidemia, nonenzymatic fructosylation of proteins, hyperlipidemia, hyperuricemia • Accumulation of uric acid by degradation of AMP • ATP depletion, ROS generation, lipogenesis, reduced NO bioavailability, endothelial dysfunction, proinflammatory cytokine secretion • Induce ectopic fat deposition
Gut microbiota	• Via the bacteria-derived butyrate, provides adaptation to hypoxic environment by impacting barrier function and survival	• Trigger dysbiosis, alter production of SCFA, disrupt tight junctions between intestinal cells • Cause endotoxemia reaching to liver by portal vein, trigger TLR signaling, contribute to steatohepatitis
Liver	• Increases mitochondria and peroxisome numbers	• Increase fatty acid accumulation leading to cell death, mitochondrial injury, ER stress, iron overload
Heart	• Induces isoform switching to KHK-C enzyme	• Lead to cardiac hypertrophy, hyperuricemia, ROS, oxidative stress, cardiac damage, hypertension, endothelial injury and vasoconstriction, increased risk of ischemia
Kidney	• Represses CPT1A to decrease mitochondrial fatty acid transport	• Lead to formation of lipid droplets as storage, therefore formation of fatty kidney disease
Immunity and cancer	• Activates the innate immune system, induces proinflammatory cytokines and chemokines • Triggers myelocyte & lymphocyte development, provides dendritic cell activation and maturation, neutrophil survival, macrophage function, increased phagocytosis	• Increase tumorigenesis by transcribing genes for glycolytic pathways, activating glucose transporters, and enhancing angiogenic factors • Increase PFKFB to override the inhibitory effect of ATP, therefore increased glucose uptake and glycolytic flux
Metabolic	• Induces isoform switching to KHK-C enzyme	• Degrade peroxisomes, cause fatty acid accumulation, disturb lipid and energy homeostasis by the activation of PPARα

HREs hypoxia-responsive elements, *KHK-C* ketohexokinase, *CPT1A* carnitine palmitoyl transferase 1A, *HIF* hypoxia-inducible factor, *AMP* adenosine monophosphate, *ATP* adenosine triphosphate, *NO* nitric oxide, *ROS* reactive oxygen species, *SCFA* short-chain fatty acids, *TLR* toll-like receptor, *ER* endoplasmic reticulum, *PFKFB* 6-phospho-2-kinase/fructose2,6-biphosphatase 1-4, *PPARs* peroxisome proliferator-activated receptors

an alpha and a beta subunit [2]. While the beta subunit is constitutively expressed and controlled in an oxygen-independent manner, the alpha subunit is maintained at low levels in most cells under normoxic conditions but is remarkably high during hypoxia [3]. In the settings of normal oxygen levels, HIF-1α is hydroxylated due to oxygen-dependent prolyl-4-hydroxylases (PHD) which results in the binding to Von Hippel–Lindau protein that then results in its ubiquitination by proteasomal degradation by E3 ubiquitin ligase. Additionally, the asparagine residues of HIF-1α are hydroxylated via factors inhibiting HIFs (FIHs) that prevent the interaction between HIF-1α and its co-activators, namely, p300/CREB-binding protein. Therefore, HIF-1α and its downstream signaling pathway are downregulated when tissues are adequately oxygenated. On the other hand, under hypoxic conditions, both FIHs and PHD are repressed, leading to translocation of HIF-1α into nucleus from cytoplasm and binding with HIF-1β.

The HIF heterodimer acts as a transcription factor that binds hypoxia-responsive elements (HREs) on hypoxia-responsive genes. This sets off a series of protective responses (Table 1). First, oxygen demands are reduced by decreasing mitochondrial function, such as by repressing carnitine palmitoyl transferase 1A (CPT1A), a rate-limiting transport system for mitochondrial fatty acid transport. To compensate for the reduction in oxygen-dependent ATP production, there is the stimulation of glucose uptake (by increasing glucose transporters) and glycolytic metabolism. Furthermore, the HIF pathway also stimulates the production of red blood cells by increasing erythropoietin, as well as stimulate new blood vessel formation (angiogenesis). The latter requires the production of metalloproteinases to remodel the extracellular matrix as well as the stimulation of the endothelium such as by stimulating vascular endothelial growth factor (VEGF) (Table 1). HIFs also activate the host defense system, such as by inducing nuclear factor-κB (NF-κB) pathway [4, 5], phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) activation via the mammalian target of rapamycin (mTOR), and RAS-RAF-mitogen-activated protein kinase kinase (MEK) via extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK)-interacting kinase (MNK) [6, 7, 8•, 9].

Thus, HIFs play an essential role in the cellular response to low oxygen, orchestrating a metabolic switch that allows cells to survive in this environment [10•]. It coordinates a transcriptional program that ensures optimal functional, metabolic, and vascular adaptation to oxygen changes [11].

Fructose, Another Major Survival Pathway

Recently, it was discovered that fructose also orchestrates a survival response to protect the animal from energy shortage. Specifically, dietary fructose, such as present in honey and fruits, is used by many animals preparing for hibernation or long-distance migration in which there is a food or water shortage. This includes stimulating hunger, foraging, increasing food intake, reducing resting energy metabolism, storing fat, becoming insulin resistant, raising blood pressure, and stimulating innate immune responses [12].

The mechanism by which fructose drives this survival response is mediated by a specific enzyme known as fructokinase C (also ketohexokinase C, or KHK-C). This enzyme metabolizes fructose rapidly, resulting in an acute fall in ATP levels that persists due to suppression of mitochondrial function with a stimulation of glycolysis [13–15]. The basis for this effect is the activation of adenosine monophosphate (AMP) deaminase, which causes the rapid removal of AMP followed by its stepwise degradation to uric acid [16] (Fig. 1). Fructose also stimulates the synthesis of uric acid from amino acid precursors [17]. In turn, the uric acid stimulates NADPH oxidases that cause oxidative stress to the mitochondria, suppressing the citric acid cycle (by inhibiting aconitase) and β fatty acid oxidation. ATP regeneration is further blocked by the inhibition of AMP-activated protein kinase by the uric acid. Glycolysis is also stimulated, first by the rapid uptake of glucose due to a fructose-1-phosphate stimulation of glucokinase, as well as by a stimulation of phosphofructokinase in response to the fall in ATP [18]. With the reduction in mitochondrial function, much of the pyruvate generated from fructose is converted to lactate [19].

Hence, fructose metabolism has marked similarities to HIF pathways, as it reduces oxygen demands by suppressing mitochondrial function and stimulating glycolysis. Indeed, fructose-dependent glycolysis has been reported to be important in how the naked mole rat survives in its hypoxic burrows [20]. Cancer cells also commonly live in hypoxic environments as they often metastasize to sites without blood supply and then need to induce angiogenesis. It is not surprising that studies show that many cancer cells prefer fructose as it can help stimulate glycolysis even when oxygen is adequate (the Warburg effect) [21, 22].

Endogenous Fructose and the Aldose Reductase System

While most studies focused on dietary fructose, fructose can also be generated in the body, and this is specific to one enzymatic process known as the polyol pathway (Fig. 1). Here, the rate-limiting enzyme is aldose reductase, which converts glucose to sorbitol, followed by the further conversion to fructose by sorbitol dehydrogenase.

Originally, the importance of the polyol pathway was thought to be limited to diabetes, as high glucose concentrations are known to stimulate aldose reductase. However, it was later shown that endogenous fructose production in

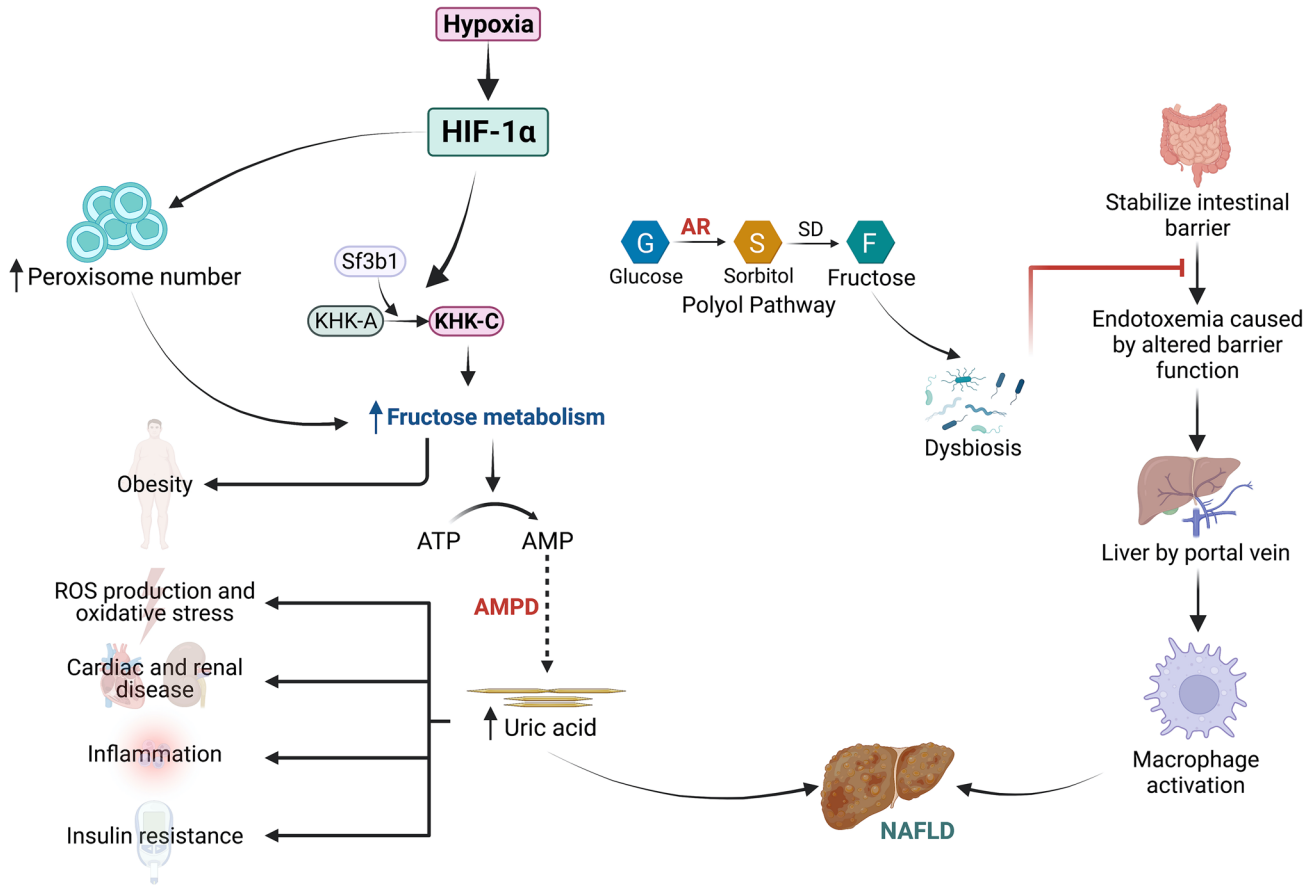

Fig. 1 Effects of HIF-1 alpha and fructose on different pathways

the liver may be an important driver of obesity and metabolic syndrome in response to high glycemic carbohydrates (which leads to high intrahepatic glucose levels that can stimulate aldose reductase) or salty foods (in which high intrahepatic osmolality stimulates aldose reductase) [23, 24]. Similarly, aldose reductase is also stimulated with hypoxia, leading to endogenous fructose production in the naked mole rat that lives in hypoxic burrows [20]. These studies emphasize the importance of fructose metabolism.

HIF and Fructose Are Coordinated in the Acute Response to Injury

It is perhaps not surprising that fructose production and metabolism can also be induced at sites of tissue injury and not just involve the whole organism. One major site where this has been shown besides the liver [23, 24] is the kidney. For example, with ischemia-mediated acute kidney injury, there is a marked increase in both local fructose production and metabolism by KHK-C [25]. The ischemia in this model is associated with a rapid reduction in local ATP levels, which persists for several days. This persistence can be shown to be mediated by fructose metabolism, as global KHK knockout mice have a more rapid return in ATP levels. While one might posit that a reduction in mitochondrial metabolism and ATP levels might be initially protective, it turns out that persistent reduction in ATP was associated with local inflammation and worse renal outcomes. Indeed, global KHK knockout mice were protected [25].

Similarly, we found evidence for endogenous production of fructose in other experimental kidney diseases in which it was likely induced by increased serum osmolality, elevated blood glucose, or ischemic injury itself [26, 27]. Indeed, since the fructose metabolism triggers xanthine oxidase activation along with both the production of oxidants and uric acid, it is very likely that fructose metabolism may be responsible for the ischemia reperfusion injury due to oxidative stress [28].

One might posit that the areas where fructose metabolism might drive hypoxia-induced inflammation should be limited to where KHK-C is expressed. Interestingly, while KHK-C is heavily expressed in the gut, liver, and kidney, it is

also expressed in the islets in the pancreas, in adipose tissue, and in the brain [29].

However, recently, it has been shown that HIF-1α can induce the expression of KHK-C in tissues that normally do not express KHK-C. KHK actually exists as two isoforms, known as KHK-A and KHK-C, which are generated through mutually exclusive alternative splicing of KHK pre-mRNAs [30]. Unlike KHK-C, KHK-A has a very low binding affinity for fructose and does not activate the survival response.

However, tissues can be induced to express KHK-C through a clever mechanism. Studies in a cardiac model of hypertension and cardiac hypertrophy found that local tissue hypoxia stimulated HIF-1α that triggered aldose reductase activity with local fructose generation [31]. However, of more interest was that HIF-1α stimulated splice factor 3b subunit 1 (Sf3b1SF3B1 that then stimulates KHK-C protein production following the preferential pre-mRNA splicing instead of KHK-A) [30–32]. This was then associated with local fructose metabolism and the HIF-1α orchestrated response, which included a suppression of mitochondrial function with a stimulation of glucose transporters (GLUT) as well as the fructose transporter, Glut5 [33], and also the glycolytic enzymes including phosphofructokinase, pyruvate kinase, and lactate dehydrogenase [31].

Again, while these findings should acutely protect tissues by reducing oxygen demands, this process was associated with cardiac modeling, left ventricular hypertrophy, and impaired relaxation of the ventricular chamber, creating the condition of preserved ejection cardiac failure. Interestingly, mice lacking fructokinase (global KHK KO) were protected and also did not show the marked shift in mitochondrial to glycolytic metabolism [31, 34, 35].

These studies suggest that the HIF1a and fructose metabolism pathways are interconnected. Since this shift in energy metabolism from mitochondria to glycolysis is also involved in the development of metabolic syndrome and kidney diseases, this also suggests that chronic HIF-1α stimulation may also have a role in these diseases.

In contrast, stimulation of HIF-1β actually represses KHK and aldolase B expression, through a mechanism that is linked with peroxisome function and involves binding to HIF-2α with the heterodimer blocking PPAR-α activation [36]. HIF-2α activation also leads to an upregulation in erythropoietin and vascular endothelial growth factor [37, 38••].

HIFs and Fructose May Work in Synergy in Metabolic Syndrome-Related Diseases

The synergistic association of HIF pathway and fructose metabolism has been observed in various medical conditions such as non-alcoholic steatohepatitis, cardiovascular events, metabolic syndrome, malignancy, chronic kidney disease, and hyperlipidemia.

For example, fructose and uric acid are well-known to have a role in non-alcoholic fatty liver disease [39], and fatty liver can also develop from foods that cause endogenous fructose production in the liver, such as from high glycemic carbohydrates or salty foods [23, 24]. However, a role for hypoxia is also likely, as non-alcoholic hepatitis is associated with HIF-1 alpha activation in hepatocytes, where it is also driving fatty acid accumulation leading to cell death which has been observed as well as mitochondrial injury, endoplasmic reticulum stress, and iron overload [40]. Indeed, HIF-1 represses carnitine palmitoyl transferase 1A (CPT1A), which is the rate-limiting component that decreases mitochondrial fatty acid transport. The reduced fatty acid transport into mitochondria enhances fatty acid to form lipid droplets as storage which eventually leads to formation of fat in both the liver and kidney [41].

Ischemia and hypoxia are also important in kidney disease, whether it be acute kidney injury or diabetic nephropathy [42, 43]. In these conditions, the ischemia is known to stimulate both HIF1 alpha activation [42, 44] and the production and increased metabolism of fructose along with the upregulation of xanthine oxidase with the production of uric acid and oxidants [25–27]. Consistent with these findings, several studies suggest that both diabetic and non-diabetic chronic kidney diseases are characterized by oxidative stress to the mitochondria, resulting in a depression of mitochondrial function and a shift to glycolysis [45–50]. Blocking fructose metabolism has also been found to improve diabetic nephropathy [27] and to prevent aging-associated kidney disease [51]. Furthermore, fructose and uric acid metabolism can lead to a reduction in endothelial nitric oxide bioavailability [52, 53] and to cause renal vasoconstriction [54, 55] that may amplify the ischemic process.

Renal hypoxia also stimulates HIF-1 that suppresses mitochondrial function and stimulates glycolysis and may also stimulate the production of fatty kidney similar to fructose metabolism [56, 57]. Indeed, there is a positive correlation between urinary liver-type fatty acid-binding protein (L-FABP) and renal HIF-1 alpha expression. Increased HIF-1 alpha is also observed with obesity, hyperglycemia, and hypertension [58].

The shift from mitochondrial to glycolytic metabolism may be protective acutely but over time leads to chronic inflammation and progressive loss of organ function [44, 59]. Indeed, it is possible that the beneficial effect of SGLT2 inhibitors on chronic disease is that it reduces glucose uptake into tissues (thereby reducing the production of fructose from glucose via the polyol pathway) [59] coupled with reducing energy supply that may force the tissues to convert to fat oxidation (such as occurs during hibernation) [60]. Indeed, SGLT2 inhibitors have been reported to improve kidney injury and fibrosis in association with reducing HIF-1 upregulation [61, 62].

HIF-1 alpha activation and stabilization and fructose metabolism also have overlapping roles in cancer. When tumor cells are exposed to hypoxia, HIF-1 alpha gets activated and stabilized to express transcription of several genes for glycolytic pathways, glucose transporters, and angiogenic factors [63]. Among the glycolytic mechanisms induced by HIF-1 alpha, PFKFB (6-phospho-2-kinase/fructose2,6-biphosphatase 1-4) is the most essential modulator of tumorigenesis as it elevates fructose-2,6-biphosphate (F-2,6-BP) levels [64]. PFKFB can override the inhibitory effect of ATP on phosphofructokinase-1, which is the major rate-limiting enzyme in glycolysis; hence, it causes increased glucose uptake and glycolytic flux [64]. Studies about brain tumors show that PFKFB3 levels are significantly higher in high-grade glioma than in healthy brain tissue lower grade gliomas [65]. In another study, PFKFB4 levels were demonstrated to be connected to the development of bladder cancer [66].

Fructose metabolism is also critical for tumor growth, as it is an ideal fuel for tumor cells living in a hypoxic environment [22], and directly can promote the Warburg effect [21]. Not surprisingly, uric acid, a byproduct of fructose metabolism, is also strongly associated with various cancers [67, 68], and uricase knockout mice show accelerated metastases when injected with tumors [69].

Association of Fructose Metabolism and HIF on Microbiota and Inflammation

In the small intestine, microbiota produces some metabolites one of them being short-chain fatty acids (SCFA). These metabolites increase oxygen consumption by intestinal epithelial cells, reducing oxygen availability in the gut and lead to hypoxia [70]. In this physiological hypoxia condition, cellular hypoxic sensors, including the hypoxia-inducible factor (HIF), are activated and provide adaptation to hypoxic environment by impacting barrier function and survival [71]. For instance, bacteria-derived butyrate which is a SCFA affects epithelial oxygen consumption and results in HIF stabilization which is coordinating the barrier protection [72]. However, excessive fructose consumption triggers dysbiosis and alters the production of SCFA which affects barrier function of the intestinal cells [73]. It can cause the disruption of the tight junctions between intestinal cells. In addition, increased fructose causes endotoxemia reaching to liver by portal vein and triggering Toll-like receptor (TLR) signaling in liver macrophages and may contribute to formation of steatohepatitis [71].

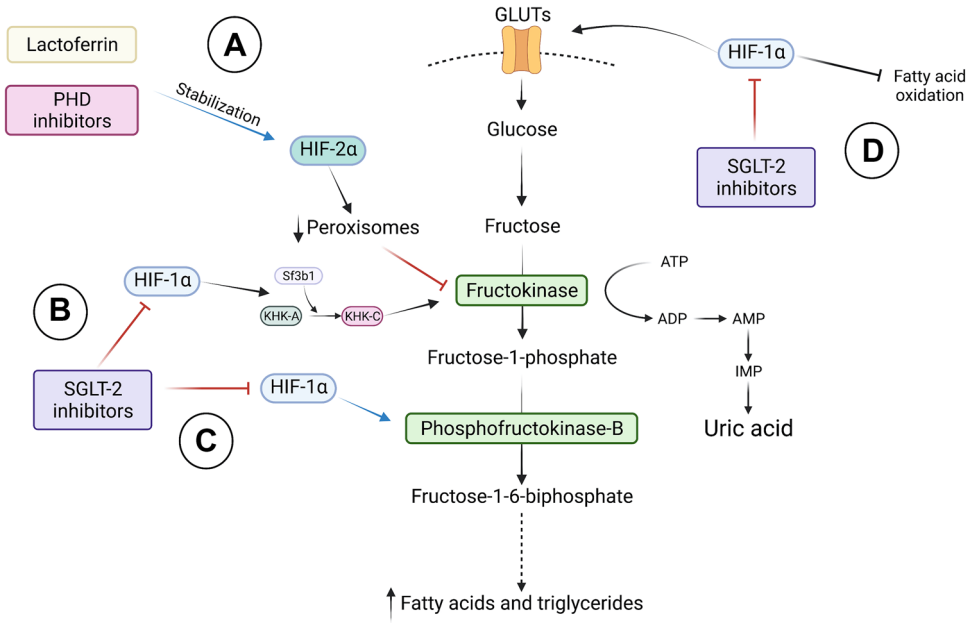

Fig. 2 Medications may be effective on hypoxia-inducible factors (HIFs) and fructose metabolism. **A** Stabilization of HIF-2a by lactoferrin and PHD inhibitors leads to decreased peroxisome number which eventually decreases fructosekinase activity and fructose metabolism. **B** KHK-A to KHK-C isoform switching via activation of Sf3b1 by HIF-1a may be inhibited by SGLT-2 inhibitors, leading to decreased fructose metabolism. **C** HIF-1a increases phosphofructokinase-B (PFKFB) activity by overriding the inhibitory effect of ATP, may be inhibited by SGLT-2 inhibitors. **D** HIF-1a activates glucose transporters (GLUTs) and increasing glycolytic pathway. SGLT-2 inhibitors may be effective to decrease glycolysis and fructose metabolism by inhibiting HIF-1a

Systemic Inflammation

Fructose also has an effect on the immune system [74]. Higher uric levels can also cause the activation of innate immune system by triggering inflammasome pathways which results in interleukin-1β (IL-1β) release and can also stimulate NF-KB and inflammasome-independent regulation [75–77]. Furthermore, HIF-1 alpha expression and stabilization in immune cells can be triggered by hypoxia which has a vital role in the induction of pro-inflammatory cytokines and chemokines which provides another aspect of immune control [10•, 11]. In addition to this, HIF also triggers myeloid cell and lymphocyte development. For instance, HIF provides dendritic cell activation and maturation, neutrophil survival and increased phagocytosis, and macrophage function as well as B cell development [10•].

Relevance to HIF Regulators

The ability of HIF-1 activators to stimulate erythropoietin production has led to the development of HIF-1 activating or stabilizing drugs [78]. Indeed, multiple clinical trials shown the benefits of HIF-1alpha stabilizers on correcting anemia in CKD patients either on dialysis or medical therapy when compared against either placebo [79–89] or EPO analogs [86, 89–93]. These clinical trials only reported minor adverse effects without any significant increase in the risk for cardiovascular events or thrombotic events [93–95].

In addition, some of these agents, such as roxadustat, have shown some promise in protecting against some acute kidney injury models [96–99], and which may lead to reduced transition to CKD [100]. Other HIF stabilizers have been reported to help block oxidative stress [101] and to reduce steatosis in liver and other organs (Fig. 2) [102, 103].

However, it is important to note that current trials have investigated the role of HIF stabilizers in short-term studies, and if chronic HIF activation and fructose metabolism are similar, these acute beneficial effects may actually lead to long-term chronic proinflammatory effects. Indeed, questions regarding the potential detrimental effects in long-term follow-up have been raised in terms of unfavorable cardiac events which requires proper addressing with future studies in this field [104–106]. Indeed, there is evidence that some protective agents, such as SGLT2 inhibitors [61, 62] and losartan [40], act in part by blocking HIF-1 activation (Fig. 2).

Conclusions

In conclusion, there is increasing evidence that inflammation is in association with activation of hypoxia-based pathways and that these include the stimulation of HIF1alpha and the activation of the polyol pathway with the production and metabolism of endogenous fructose. The acute stimulation of these pathways protects tissues from hypoxia by decreasing oxygen demands via the suppression of mitochondrial function and the stimulation of glycolysis. While these effects are beneficial in the immediate short-term, over time, they may be the cause of chronic inflammation and fibrosis. SGLT2 inhibitors may provide benefit by blocking this process, while HIF1alpha stabilizers may improve hematocrit but carry the potential for worsening disease progression. More studies are needed to understand the complexity and interactions of these two important pathways.

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Code Availability Not applicable.

Compliance with Ethical Standards

All figures are drawn by the authors. No need to have any permission from other sources.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest Richard J. Johnson and Miguel A. Lanaspa have equity with Colorado Research Partners LLC that is developing inhibitors of fructose metabolism. Dr Johnson also has stocks with XORTX Therapeutics and has received honoraria from Horizon Pharma. All other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors. Not applicable (as this is review article, no human or animal consent is needed).

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- • Of importance
- •• Of major importance

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