Communication

The Regulatory Mechanism of SGLT2 Inhibitors on Liver Fibrosis: An Integrated Hypothesis of 'Metabolic Hijacking and Energy Crisis'

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Posted Date: 13 August 2025

doi: 10.20944/preprints202508.0991.v1

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The Regulatory Mechanism of SGLT2 Inhibitors on Liver Fibrosis: An Integrated Hypothesis of 'Metabolic Hijacking and Energy Crisis'

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially developed for type 2 diabetes, have unexpectedly demonstrated significant anti-fibrotic effects in non-alcoholic steatohepatitis (NASH), presenting a paradigm shift in hepatology. However, the underlying mechanism remains a critical paradox, as SGLT2 expression is nearly absent in the healthy liver parenchyma. Prevailing hypotheses centered on indirect systemic metabolic improvements fail to fully account for the direct and rapid molecular changes observed within the liver. This review aims to bridge this knowledge gap by proposing a novel, unifying hypothesis. We posit that within the pathological microenvironment of liver fibrosis, a profound cellular crosstalk initiates a phenotypic switch in non-parenchymal cells like liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs). We propose that pro-inflammatory cytokines (via NF-κB) and the concomitant hypoxic stress (via HIF-1α) collaboratively drive the transcriptional upregulation of SGLT2. This 'metabolic hijacking' occurs in parallel with a HIF-1α-driven shift to glycolysis, creating a state of 'metabolic vulnerability' where cells become exquisitely dependent on this new glucose supply line. Consequently, we argue that SGLT2 inhibitors exert their direct anti-fibrotic effects by exploiting this vulnerability. By blocking this crucial glucose supply, the inhibitors precipitate a severe 'energy crisis' specifically within activated LSECs and HSCs. This acute energy deficit activates the master energy sensor, AMP-activated protein kinase (AMPK), which orchestrates a dual restorative response. AMPK directly enhances endothelial nitric oxide synthase (eNOS) phosphorylation to restore NO bioavailability, while also suppressing HIF-1α in a self-amplifying feedback loop that dismantles the pro-fibrotic metabolic program. This model provides a comprehensive, cell-specific mechanism that integrates inflammation, hypoxia, and metabolic reprogramming to explain the direct and sustained therapeutic action of SGLT2 inhibitors in liver fibrosis.

Keywords: SGLT2 inhibitor; LSEC; Liver fibrosis

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, affecting over 25% of the global adult population [1–3]. A subset of patients progress to non-alcoholic steatohepatitis (NASH), which involves hepatocellular injury and chronic inflammation, serving as a key driver of liver fibrosis [4,5]. Despite its potential to advance to cirrhosis and hepatocellular carcinoma [6,7], there are currently no FDA-approved anti-fibrotic therapies [8–10]. Amidst this significant unmet medical need, the finding that SGLT2 inhibitors significantly improve liver fibrosis has offered new hope [11–13].

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Multiple randomized controlled trials have reported that SGLT2 inhibitors not only reduce hepatic fat content [14,15] but also improve fibrosis markers [14,16]. This phenomenon, however, presents a significant biological paradox, as SGLT2 is virtually unexpressed in the normal liver parenchyma [16]. Initial hypotheses centered on 'indirect effects,' suggesting that systemic metabolic improvements provide secondary benefits [17,18]. While plausible, this falls short of fully explaining the direct and rapid molecular changes observed within the liver tissue.

This explanatory gap necessitates a shift in perspective. Liver fibrosis is driven by dynamic interactions between non-parenchymal cells, especially liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs) [19,20]. LSEC dysfunction is a critical early event that precedes HSC activation [21,22]. Therefore, to unravel the mystery of SGLT2 inhibitors, a new approach focusing on LSECs and HSCs is required. Accordingly, this review proposes a new, unifying hypothesis centered on these cells: the 'Metabolic Hijacking and Energy Crisis' model, which is further deepened by considering the roles of hypoxia and cellular metabolic state [23–25].

2. The 'Metabolic Hijacking and Energy Crisis' Hypothesis

To address the existing paradox, we propose the 'Metabolic Hijacking and Energy Crisis' model. This model pivots the focus to LSECs and HSCs as the primary targets of SGLT2 inhibitors. It is built upon two core pillars, now expanded to incorporate the crucial role of hypoxia-inducible factor 1-alpha (HIF-1α).

2.1. Hypothesis 1: Pathological Induction of SGLT2 and Metabolic Vulnerability ('Metabolic Hijacking')

We first propose that the chronic inflammatory and hypoxic milieu is the direct cause for the ectopic expression of SGLT2 and the simultaneous induction of a metabolically vulnerable state.

Scientific Rationale and Evidence:

1. **SGLT2 is Indeed Upregulated in the Fibrotic Liver, Primarily in LSECs:** Groundbreaking work has demonstrated that SGLT2 expression, absent in the healthy liver, is significantly induced in the LSECs of cirrhotic rat models and human NASH patients [26–28]. This firmly establishes that SGLT2 becomes a tangible molecular entity in the diseased liver, localized specifically to the cells driving fibrosis.
2. **Pro-fibrotic Cytokines and NF-κB as the Inflammatory Switch:** The fibrotic microenvironment is saturated with pro-inflammatory cytokines like TNF-α and TGF-β [29–31]. We postulate that the NF-κB signaling pathway, a master regulator of inflammation activated by these cytokines, acts as a central transcriptional switch mediating SGLT2 expression. This is supported by evidence showing TGF-β1 increases SGLT2 expression [32] and the known functional regulatory loop between the SGLT2 axis and NF-κB [33].
3. **Hypoxia and HIF-1α as a Critical Co-factor:** The fibrotic liver is inherently hypoxic [34–37]. This condition stabilizes Hypoxia-Inducible Factor 1-alpha (HIF-1α)[38,39] , the master regulator of the cellular response to low oxygen [40–42]. We propose that HIF-1α acts as a crucial co-conspirator with NF-κB. It is highly plausible that HIF-1α and NF-κB synergistically bind to the *SLC5A2* gene promoter, leading to a maximal, robust expression of SGLT2 that neither inflammation nor hypoxia could achieve alone.
4. **Creation of 'Metabolic Vulnerability':** Crucially, HIF-1α's primary role is to enforce a **'glycolytic switch,'** reprogramming cellular metabolism from efficient mitochondrial respiration to rapid, but inefficient, glycolysis [43]. This makes the activated LSECs and

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HSCs "glucose addicts," critically dependent on a high flux of glucose to fuel their energy-demanding pro-fibrotic functions. Therefore, the pathological environment doesn't just induce a new transporter; it fundamentally rewires the cell's metabolism, creating a profound 'metabolic vulnerability' where survival is precariously tethered to the function of the hijacked SGLT2.

2.2. Hypothesis 2: Therapeutic Exploitation via an 'Energy Crisis' and a Dual Restorative Response

Building on this, we propose that the therapeutic action of SGLT2 inhibitors is mediated by exploiting this induced vulnerability, triggering an 'energy crisis' that activates a powerful, dual-action restorative program.

Scientific Rationale and Evidence:

1. **Induction of an 'Energy Crisis' and AMPK Activation:** By blocking their primary hijacked glucose transporter, SGLT2 inhibitors effectively cut off the main fuel supply to these glycolytically-dependent cells. This leads to a sharp decrease in intracellular ATP and a corresponding increase in the AMP/ATP ratio. This metabolic shift is a potent activator of the master energy sensor, AMP-activated protein kinase (AMPK) [44,45].
2. **The AMPK-Orchestrated Dual Response:** Once activated, AMPK acts as a master switch, initiating two distinct but complementary restorative arms:
    - **The Effector Arm (Restoring Endothelial Function via eNOS/NO):** A critical consequence of AMPK activation in endothelial cells is the phosphorylation and activation of endothelial nitric oxide synthase (eNOS), leading to the production of nitric oxide (NO) [46–49]. NO is the most critical paracrine signal for maintaining LSEC health and HSC quiescence. In the fibrotic liver, eNOS activity is dramatically reduced [50–52]. SGLT2 inhibitors, by activating AMPK, restore eNOS phosphorylation and NO production, thereby reversing LSEC capillarization and suppressing HSC activation [53,54]. This arm directly tackles the physical and functional deterioration in fibrosis.
    - **The Reinforcing Arm (Dismantling the Metabolic Program via HIF-1α):** Simultaneously, AMPK acts to dismantle the underlying metabolic pathology. Activated AMPK is a known negative regulator of HIF-1α, promoting its degradation [55,56]. By eliminating the master regulator of the 'glycolytic switch,' AMPK breaks the cell's addiction to glucose [57,58]. This creates a self-amplifying feedback loop: as HIF-1α falls, the cell's glycolytic program falters, making it even more reliant on the inhibited SGLT2 pathway. This progressively enhances the drug's efficacy, providing a mechanism for sustained and potentially amplifying therapeutic effects over time.

3. Discussion

The 'Metabolic Hijacking and Energy Crisis' hypothesis, enriched by the roles of HIF-1α and AMPK, offers a comprehensive solution to the SGLT2 inhibitor paradox. Its originality lies in shifting the focus from hepatocytes to the non-parenchymal cells and, more importantly, from the mere presence of a drug target to the disease-induced metabolic state that makes the target relevant.

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The key insight is that the drug's target is not a static molecule but a dynamic, 'disease-induced state of vulnerability'. The model's strength lies in its balanced integration of multiple pathways. It gives equal weight to the immediate, functional restoration of the endothelium via the AMPK-eNOS-NO axis and the sustained, reinforcing effect of dismantling the pro-fibrotic metabolic program via the AMPK-HIF-1α axis. This dual mechanism provides a more robust explanation for both the rapid and the long-term clinical benefits observed with SGLT2 inhibitors. Furthermore, the concept of a self-amplifying loop explains how the therapeutic effect could be magnified over the course of treatment, a phenomenon that simpler models cannot account for.

4. Gaps in Knowledge and an Experimental Roadmap for Validation

While this integrated model is robust, its tenets require rigorous validation. We propose the following experimental roadmap:

- **Phase 1: Validating the Induction of Metabolic Vulnerability**
  - **Experiment 1a (Dual Signal Integration):** Use ChIP-seq in LSECs exposed to both inflammatory cytokines and hypoxia to confirm the co-localization of NF-κB and HIF-1α on the *SLC5A2* promoter.
  - **Experiment 1b (Metabolic Phenotype):** Confirm the glycolytic switch in fibrotic LSECs/HSCs using Seahorse analysis. Show that this phenotype is dependent on both NF-κB and HIF-1α using specific inhibitors or siRNAs.
- **Phase 2: Validating the Dual Restorative Response**
  - **Experiment 2a (Dissecting the AMPK Arms):** In SGLT2 inhibitor-treated cells, assess the kinetics of eNOS phosphorylation and HIF-1α degradation. Use an eNOS inhibitor (e.g., L-NAME) to test if it blocks the immediate anti-fibrotic effects, and use HIF-1α overexpression to test if it confers resistance to the long-term effects.
  - **Experiment 2b (Loop Confirmation):** Conduct time-course and dose-response experiments to test for the predicted self-amplifying effect, showing that the drug's potency increases with prolonged exposure. This can be validated by disrupting the loop with an AMPK inhibitor.
- **Phase 3: Demonstrating Therapeutic Translation**
  - **Experiment 3a (Biomarker Correlation):** In clinical cohorts, investigate whether baseline markers of inflammation (e.g., hs-CRP), hypoxia/glycolysis (e.g., plasma lactate), or endothelial dysfunction correlate with the magnitude of therapeutic response to SGLT2 inhibitors.

5. Conclusion

In conclusion, this review proposes that the anti-fibrotic efficacy of SGLT2 inhibitors is a direct consequence of a sophisticated biological process. The pathological microenvironment of the fibrotic liver, through the combined forces of inflammation and hypoxia, induces a profound 'metabolic vulnerability' in key effector cells like LSECs and HSCs. SGLT2 inhibitors masterfully exploit this vulnerability, activating AMPK to orchestrate a powerful dual restorative response that both repairs endothelial function via the eNOS/NO axis and dismantles the underlying pro-fibrotic metabolic program via the HIF-1α axis. This balanced, integrated model resolves the central paradox of the

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drug's action and provides a compelling new framework for understanding and treating chronic fibrotic diseases.

6. Statement on AI Collaboration

The initial conceptualization and core hypotheses presented in this manuscript were proposed by the human authors. The subsequent literature search and evaluation of these hypotheses were conducted using Liner (Liner, Republic of Korea) an AI-powered research platform. The final composition, drafting, and refinement of the manuscript were performed through an iterative, collaborative process between the human authors and a large language model (Gemini 2.5 Pro, Google). The human authors directed all stages of the project, critically reviewed all AI-generated contributions for scientific accuracy and integrity, and take full responsibility for the final content of this paper.

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