Review

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Review

Convergent Mechanisms of Metabolism-Based Therapeutics in MASH: Mechanistic Review of SGLT2 Inhibitors and GLP-1 Receptor Agonists

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Abstract

Metabolic dysfunction-associated steatohepatitis (MASH) is a multifaceted disorder with an unmet need for effective pharmacotherapies. The emergence of two classes of anti-diabetic agents, SGLT2 inhibitors and GLP-1 receptor agonists, are now widely acknowledged as frontrunners of therapeutic options for MASH, and they have both also been shown to have durable, actionable anti-fibrotic biology. They also appear to engage disparate primary mechanisms of action, raising new questions about their commonality behind therapeutic efficacy. In this review, we propose an integrated hypothesis that places AMP-activated protein kinase (AMPK) as the master convergent node for MASH therapeutics. We suggest that the two drug classes act through discrete upstream pathways to activate AMPK. Both SGLT2 inhibitors and GLP-1 receptor agonists activate AMPK, but SGLT2 inhibitors appear to preferentially engage an LKB1-dependent energy crisis to upregulate AMPK, while GLP-1 receptor agonists engage a CaMKKβ-dependent hormonal signal. While still exerting the same ultimate reach of activating AMPK, their differential activation of AMPK results in differential downstream effects; SGLT2 inhibitors engage cell-intrinsic stress responses such as inflammation and autophagy, whereas GLP-1 receptor agonists primarily regulate systemic and cellular lipid metabolism. Furthermore, we detail the unique, cell-type selective, and epigenetic mechanisms of SGLT2 upregulation in the fibrotic liver which eclectically provide molecular mechanistic rational for the SGLT2 inhibitors' direct hepatic action pathways. Once again, our integrated model resolves unanswered paradoxes for each drug class, but also creates a strong mechanistic rationale for the application of precision medicine and rational synergies of combination therapies for MASH.

Keywords: GLT2 inhibitor; LSEC; Liver fibrosis; GLP-1 analogue

1. Introduction

1.1. The Clinical Challenge of MASH and Liver Fibrosis

Metabolic dysfunction-associated steatohepatitis (MASH) [1] denotes the progressive, inflammatory phase of a broad spectrum of conditions commencing with liver fat accumulation (steatosis) and has quickly become one of the leading causes of chronic liver disease globally, similar to obesity and type 2 diabetes, both of which are global epidemics [2–5]. While simple steatosis is usually an inconsequential disease [6,7], the crucial juncture is when simple steatosis progresses to MASH. Progression from steatosis to MASH occurs when hepatic fat accumulation coexists [8,9]with hepatocellular injury (ballooning) and inflammation, a clinical spectrum known as steatohepatitis. Chronic inflammation results in a wound healing response that over time becomes pathological

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[10,11]. This chronic inflammatory response ultimately results in excessive accumulation of extracellular matrix proteins, leading to the development of connective tissue scar (fibrosis) [12–16]. Liver fibrosis is the most critical determinant of long-term outcomes and risk of mortality in patients diagnosed with MASH [12,17–19]. Fibrosis progresses from mild (F1) to cirrhosis (F4), with the risk for developing hepatic failure, portal hypertension, and hepatocellular carcinoma accelerating steeply the deeper a patient progresses into the fibrosis continuum [20,21]. Despite the compelling clinical need, there have been no anti-fibrotic medications that have been approved by regulators [21,22].

1.2. The Emergence of Two Metabolic Powerhouses: SGLT2 Inhibitors and GLP-1 Receptor Agonists

In this challenging treatment area, two major pharmacological classes of drugs, initially developed for type 2 diabetes, have proven to be an unanticipated but potent major solution for MASH and liver fibrosis [23–26].

- **Sodium-glucose cotransporter 2 (SGLT2) inhibitors** (e.g., empagliflozin, dapagliflozin), act primarily on the kidney, inhibiting the reabsorption of glucose from the renal filtrate into the systemic circulation, increasing urinary glucose excretion to lower blood sugars [27–29].
- **Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs)** (e.g., semaglutide, liraglutide), also known as incretin mimetics, mimic the actions of the endogenous gut hormone GLP-1, enhancing glucose-dependent insulin secretion, inhibiting glucagon secretion, slowing gastric emptying, and acting on the central nervous system to improve satiety resulting in substantial effective weight loss [30–32].

Very well designed, randomized, controlled clinical trials have shown that both classes of drugs can improve liver histology, and some trials report reversal of fibrosis as well [33–36].

1.3. The Central Mechanistic Questions

While both SGLT2 inhibitors and GLP-1 RAs produce similar clinical benefits, they do so via very different primary modes of action. This shared therapeutic outcome presents some fundamental mechanistic questions that we will address in this review:

1. **The SGLT2 Expression Paradox:** SGLT2 inhibitors produce effects on the liver, but SGLT2's target in the healthy state (the SGLT2 receptor) is virtually absent [37]. How do SGLT2 inhibition and drug action occur in the context of the liver?
2. **The HIF-1α Paradox:** The SGLT2 inhibitors are effective in the hypoxic fibrotic liver; however, studies indicate that hypoxia and HIF-1α as the master regulator of hypoxia, decrease SGLT2 expression in other cell types such as renal and pancreatic cells [38,39].
3. **The Convergence question:** How do these two distinct pharmacological interventions converge on the same therapeutic endpoint of fibrosis resolution? The GLP-1 RA approach primarily induces systemic metabolic benefits through hormonally driven weight loss, while the SGLT2 inhibitor approach, in addition to modest weight loss via glucosuria, is hypothesized to exert a direct hepatic effect by provoking a cellular 'energy crisis' [40].

This review will try to create a coherent mechanistic model, addressing these queries. We will first elucidate a detailed, elaborative, multi-stage model explaining cell-type and epigenetically regulated SGLT2 in the fibrotic liver, then place AMPK as the primary converging hub and posit a mechanistic model explaining SGLT2 inhibitors and GLP-1 RAs converge on a common conspicuous node, via different upstream pathways (i.e., lower energy ln deficiency of glucose influx as directed by SGLT2 inhibition vs hormonal signal directed by GLP-1 RA), to achieve complementary therapeutic downstream actions.

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2. The SGLT2 Inhibitor Axis: A Story of Cell-Specific Adaptation and Epigenetic Pathology

To appreciate the action of SGLT2 inhibitors it would be prudent to better understand how the target of the drug becomes pathologically relevant in the diseased liver. We believe this is not quite as simple as an "on/off" event, but rather activity stimulated in this organ through a process which entails two steps mediated by different cell types and signal regulators.

2.1. Stage 1: Adaptive Response - Hepatic and LSEC SGLT2 Upregulation During Liver Injury

In the early phases of liver injury i.e., metabolic stress, inflammation and/or hypoxia, we suspect that SGLT2 upregulation is not an error but rather a unique, liver-specific adaptive response in the setting of liver injury. In the case of stress in the role of glucose regulating hepatocytes, the liver is no longer the body's glucose regulator (as it does in healthy systemic metabolism), but it is challenged as the central glucostat of the body which actively senses glucose and manages glucose flux to maintain systemic glucose regulation. Stress conditions likely diminish this capability. We suggest that the liver injury signals of inflammation and hypoxia, converging on the SGLT2 gene promoter, form a combination of cellular pressure unique to hepatocytes and LSEC so that the issues of cell-type specificity become important to consider. HIF-1α may act to repress SGLT2 in renal cells [41], but the hepatic cellular transcriptional context permits HIF-1α - NF-κB cooperative activation of SGLT2. This induced expression provides the stressed liver another means of managing glucose flux and endothelial function, as part of specifically, we recount the pathways:

- **VEGF Signaling and LSEC Capillarization:** Normal LSECs feature pores called fenestrae that permit exchange of solutes between the blood and hepatocytes [42,43]. There is an active maintenance of this phenotype with Vascular Endothelial Growth Factor (VEGF) signaling [44,45]. In the diseased liver the accompanying impaired hepatocyte function results in reduced VEGF production. In this state deprived of VEGF signaling, the LSECs undergo a pathological transformation known as 'capillarization' where the fenestrae are lost and a continuous basement membrane is formed which prevents molecular exchange and supports the development of portal hypertension [46–49]. This alteration to the LSECs is also a pivotal initiating event in fibrosis [50].
- **Inflammation and NF-κB Activation:** The MASH liver features a chronic sterile inflammatory state [51]. The lipotoxicity and cellular injury causes damage-associated molecular pattern (DAMPs) release and the priming of resident immune cells such as Kupffer cells [52,53]. Kupffer cells in this condition release a wave of pro-inflammatory cytokines e.g. Tumor Necrosis Factor-alpha (TNF-α) and Transforming Growth Factor-beta (TGF-β) [54,55]. These cytokines act on surrounding cells, including LSECs and hepatocytes, causing expression of the master inflammatory transcription factor, nuclear factor-kappa B (NF-kB) [56–58]. Once activated NF-kB can regulate the expression of many genes that lead to inflammation and cell survival [59,60].
- **Hypoxia and HIF-1α Stabilization:** The capillarization of LSECs and destruction of liver parenchyma, which serves to impede blood flow and oxygen delivery, leads to a state of chronic hypoxia [61,62]. This leads to a rapid accumulation of hypoxia-inducible factor 1-alpha (HIF-1α), the transcription factor largely responsible for the cell's response to low oxygen [63,64]. In normoxic conditions, HIF-1α is continuously produced in a dynamic state, being made as quickly as it is tagged for degradation [65]. The switch to hypoxia blocks this process and allows for rapid accumulation of HIF-1α [66], which can then translocate to the nucleus to initiate expression of genes that support adaptation to low oxygen [67], most importantly

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shifting metabolism to glycolysis [68,69].

We propose that these three pathways converge. We hypothesize that the compounded pressure of NF-kB (thanks to inflammation) and HIF-1α (in response to hypoxia) will exert unique effects to promote the expression of the SGLT2 gene promoter robustly and in a liver specific manner as a compensatory mechanism.

2.2. Stage 2: The Pathological 'Lock-in' - SGLT2 Activation Through Epigenetic Mechanisms in HSCs

As chronic injury continues and the profibrotic activation of HSCs results in continued tissue injury, the regulatory framework shifts from adaptable to pathological lock-in. The epigenetic activation of SGLT2 is a key event in the transformation of quiescent HSCs into rapidly proliferating and collagen secreting myofibroblasts, an extreme phenotype switch. [70] and requires a large and extended energy source [71–73]. HSCs must reprogram their metabolism to use glycolysis as a fuel source, and permanently develop, and use glucose transporters [74]. We propose they do this through epigenetics, with interaction of chemical modifications (acetylation and methylation) of the DNA itself, or the associated proteins (histones) making gene less or more accessible. We suggest that HIF-1α is recruiting the BRG1 chromatin modelling complex to the SGLT2 locus [75]. BRG1 is like a molecular bulldozer using ATP to slide nucleosomes given away and expose the gene [76,77]. This complex likely recruits the enzymes which place "go" signals (active histone marks are H3-acetylation) to the histones surrounding SGLT2 [78,79]. This results in a so-called epigenetic "lock-in" at SGLT2 and it's permanently caved in open and active state, constructed and hardwired in HSC core fibrogenic program.

3. A Unified Therapeutic Framework: AMPK as the Central Convergent Node

Central Role of AMPK The mechanism of action of both SGLT2 inhibitors and GLP-1 RAs can both be theoretically summarized through AMPK acting as the central focus for their metabolic action [80]. AMPK is a master energy sensor for the cell [81,82]. It is activated in situations of energetic demand (high AMP to ATP ratio) and functions to return balance by inhibiting energy requiring processes and initiate energy producing systems [83–85]. In this fashion, we propose that both SGLT2 inhibitors and GLP-1 RAs activate AMPK, albeit in fundamentally different upstream pathways.

3.1. The SGLT2 Inhibitor Pathway: LKB1-Mediated Activation Targeting Cell-Intrinsic Stress

As SGLT2 inhibitors completely block glucose from entering the pathologically reliant LSECs and activated HSCs, this induces an acute and direct cellular 'energy crisis.' The acute increase in the intracellular AMP/ATP ratio is the primary signal for the upstream kinase, LKB1 [86]. In this context, we consider that SGLT2 inhibitors cause the initial AMPK activation to be predominantly LKB1 dependent. When AMPK is activated by this direct energy-stress signal, AMPK preferentially regulates critically involved cellular stress responses [87–89]. This includes:

- **Suppression of the NLRP3 Inflammasome:** The NLRP3 inflammasome is a multi-protein complex that is activated during cellular stress, which then initiates a strong inflammatory cascade. By inhibiting this pathway, AMPK attenuates the sterile inflammatory response driving MASH [90].
- **Promotion of Autophagy:** Autophagy is a cellular quality-control process that can engulf and recycle defective organelles as well as toxic lipid droplets [91,92]. By promoting autophagy as a response, AMPK clears some of the cell's debris of lipotoxicity [93,94]. Promoting autophagy represents a direct cell-intrinsic pathway to correct the core pathology of MASH.

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3.2. The GLP-1 Receptor Agonist Pathway: CaMKKβ-Mediated Activation Targeting Systemic and Lipid Metabolism

In the opposite way from SGLT2 inhibitors, GLP-1 RAs do not initiate an energy crisis. They act like hormonal signals by binding to their respective receptors, and leading to an increase in intracellular Calcium (Ca^{2+}) concentration [94,95]. This unique signal therefore, activates a different upstream kinase, Ca^{2+}/ calmodulin-dependent protein kinase kinase β (CaMKKβ); resulting in phosphorylation/activation of AMPK [96–98]. This initiation of AMPK activation through CaMKKβ activation is via hormonal means, not energy depletion, thus preferentially impacting metabolic programming, versus cellular stress response, although they are linked.

- **Suppression of De Novo Lipogenesis:** AMPK phosphorylates and inhibits key enzymes like ACC, shutting down the synthesis of new fats in the liver.
- **Promotion of Fatty Acid Oxidation:** AMPK activates enzymes like CPT1α, promoting the burning of existing fats for energy.

Lastly, the significant weight loss attributable to GLP-1 RAs is also a separate pathway that is heavy-handed [99,100]. The substantial weight loss is a major contributing factor in the systemic 'caloric restriction-like' state [101], which also activates AMPK (via systemic effects) and SIRT1 after epigenetic reprograming of HSCs .

4. Discussion

This integrated model provides powerful rationale for the future of MASH therapy, which is apt to be characterized by precision medicine and combination methods.

1. A Framework for Precision Medicine: The different downstream effects of these two classes of medication suggest an unambiguous avenue for personalized therapy. Patients with a predominantly inflammatory MASH phenotype, with high inflammatory markers, may derive a larger therapeutic effect from the robust cell-intrinsic, anti-inflammatory, and pro-autophagic actions of SGLT2 inhibitors vs patients whose MASH phenotype is predominantly metabolic and comprise obese patients with severe steatosis and dyslipidemia, who might receive more therapeutic effects from GLP-1 RAs via robust systemic weight loss and measures against lipogenesis.

2. A Rationale for Synergistic Combination Therapy: The most exciting implication of this model is the possibility of synergy. Since these two classes of medications activate the central AMPK node, through exclusive upstream pathways, there is likely strong synergy, rather than simply additive effects in combination. The reasoning here supports a "two-pronged" activation of AMPK and may produce a stronger, more sustained, and more collaborative therapeutic effect in providing combined cell-intrinsic inflammation reduction and systemic metabolic dysregulation. This provides an excellent mechanistic basis for the combination therapy studies that the field is currently awaiting with great anticipation.

5. Future Directions

To confirm this comprehensive model will require comparative experimentation to elucidate the unique and overlapping pathways of these two drug classes

- **Phase 1 & 2 (Validating the SGLT2 Axis):** Pharmacological experiments validating the cell-type-specific regulation of SGLT2, and the HIF-1α-BRG1 epigenetic lock-in in HSCs are essential foundational studies.
- **Phase 3 (Validating the Unified AMPK Model):**
  - **Experiment 3a (Upstream Dependency):** he hair factor experiment is to pharmacologically inhibit LKB1 and CaMKKβ with specific pharmacological inhibitors -- or utilize siRNA to knockdown the kinase in primary liver cells. The hypothesis predicts

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the AMPK-activating effects of SGLT2 inhibitors will be blunted with LKB1 inhibition (but not will not be blunted if LKB1 is absent), while the effects of the GLP-1 RAs will be blunted with CaMKKβ inhibition (but not be blunted if CaMKKβ is absent).

- **Experiment 3b (Downstream Profiling):** Rabbit MASH animal models, with or without hepatocyte ablation, will be treated with an SGLT2 inhibitor, a GLP-1 RA, or a combination therapy. After pharmacological intervention, the liver cells (hepatocytes, LSECs, HSCs) can be isolated to undergo multi-omic analyses (transcriptomics, proteomics, metabolomics) to confirm that SGLT2 inhibition preferentially activates inflammatory and/or autophagy pathways while GLP-1 RAs preferentially activate pathways regulating lipid metabolism.
- **Experiment 3c (Synergy Confirmation):** We can formally test for synergy in both in vitro and in vivo models, utilizing either the Bliss independence model or the Loewe additivity model. This would allow us to confirm that the combined effect of both drugs on key endpoints (i.e. fibrosis score, AMPK phosphorylation) was mathematically greater than the additive effect of each drug alone.

6. Conclusion

In conclusion, we have articulated an integrated, comprehensive model of the action of leading metabolism-based therapies in MASH. We suggest SGLT2 inhibitors operate on a target that becomes pathologically relevant by a two-stage process involving an adaptive response and then epigenetic lock-in. We position AMPK as the central therapeutic node, which is activated by SGLT2 inhibitors and GLP-1 RAs through distinct pathways that are either LKB1-dependent and CaMKKβ-dependent, respectively. This leads to complementary downstream effects on cell-intrinsic stress and systemic metabolism and provides a powerful mechanistic rationale for both precision medicine and synergistic combination therapy. This model solves existing paradoxes and provides a clear and testable plan for the future of MASH therapeutics.

7. 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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