

Review Article

The Conserving Cell: A Unified Hypothesis of Metabolic Restoration and Fragile Systems

Christopher Ryan Mearns¹

1. Independent researcher

Why can metabolic dysfunction persist in a body with abundant fuel, and why does reducing the original stress not always restore normal function? We propose that energetic burdens can shift cellular regulation toward immediate protection while limiting the restoration needed for future demands. During stress, cells change how they process fuel and allocate resources to preserve essential functions. Yet surviving a challenge does not necessarily replenish depleted materials, repair damaged machinery, or restore the capacity needed for the next demand. When challenges recur before restoration is complete, a conserving cell may become a fragile cell. If neighboring cells can no longer compensate, cellular limitations can impair tissue function and alter the support that other organs receive.

This hypothesis connects whole-body energy balance and insulin-mediated fuel distribution with the capacity of cells to maintain, repair, and coordinate their work. It brings cellular defense and restoration into the same sequence, asking what prevents recovery between challenges and how that failure could affect tissues and the wider system. Ketohexokinase-dependent fructose metabolism provides one measurable way to investigate processing costs and test whether reducing a recurring burden improves subsequent function. The full proposed progression remains unvalidated. We outline experiments that distinguish continuing injury from incomplete restoration and test whether correcting an identified limitation improves later cellular, tissue, and system performance. If shared barriers to recovery contribute to several disease outcomes, identifying them could redirect research toward restoring function across those outcomes, rather than assuming each requires a separate explanation.

Corresponding author: Christopher Ryan Mearns, chris@liv3health.com

The conserving cell

A body can have abundant fuel while some of its cells struggle to carry out their work. Removing a stress can also improve immediate conditions without returning a tissue to its previous function. These puzzles draw attention to what happens between surviving a challenge and becoming ready for the next one. During stress, a cell may restrict incoming substrate, reduce specialized activity, or redirect molecular synthesis toward defense. We call this viable, altered state a *conserving cell*. The term describes a change in priorities, not necessarily a fall in total metabolism. The question is what those priorities preserve now and what they leave to restore later.

Protection and restoration are different jobs. A cell may remain alive without replacing damaged components, replenishing depleted materials, or recovering its ability to increase output when needed. Ordinary work continues while those jobs are unfinished, and another challenge may arrive before they are complete. We propose that this overlap can turn an initially protective adjustment into lasting vulnerability. The relevant burden need not be a single large insult: recurring demands may repeatedly use the same limited capacity or interrupt the same restorative process. Inherited differences can change the capacity available to meet those demands; they need not themselves be recurring exposures.

The difference between functioning at rest and recovering after challenge is visible in an inflammatory kidney-injury model. Mice lacking PGC-1 α , a regulator of mitochondrial function, in proximal-tubule cells had no major baseline renal functional deficit but showed more persistent impairment after injury. In wild-type kidneys, PGC-1 α and selected metabolic transcripts fell during injury and rose during recovery. A separate experiment in human tubular cells found that increased PGC-1 α counteracted cytokine-associated respiratory suppression [\[1\]](#). The genetic comparison cannot separate initial susceptibility from recovery, but it shows why baseline function alone is insufficient: a regulatory program relevant to mitochondrial function can matter when the organ has to recover.

Whole-body energy balance and insulin action remain essential to this account. Calorie balance describes how much energy enters the body, is stored, and is expended. Insulin and other transport controls help determine where fuel goes. Neither question, by itself, tells us what it costs a particular cell to process that fuel, which work receives priority during stress, or whether the materials and machinery needed for later work have been restored. The proposed synthesis connects these levels over time: fuel must reach a cell, be processed, support present work, and leave enough capacity for maintenance and renewal. A later demand can reveal which part of that sequence remains constrained.

Intake is itself regulated: altering hypothalamic AMP-activated protein kinase (AMPK), an energy-sensitive regulator, changed feeding in mice ^[2]. We propose that unresolved energetic or stress-signaling disturbances in appetite-control circuits could help sustain hunger despite abundant stored fuel, increasing intake and renewing the burden. This would connect a cellular state to positive energy balance rather than contradict caloric accounting. It does not establish that human cravings measure cellular ATP, or that all overeating begins with an energetic deficit.

Insulin resistance presents a related apparent contradiction. More fuel need not improve work if processing it produces excessive stress. Experiments linking mitochondrial superoxide to impaired insulin-responsive glucose transport support an interpretation of restricted uptake as protective in those settings ^[3]. A locally protective restriction can impair whole-body fuel regulation. The distinction is between admitting substrate and restoring the capacity to handle it, not between insulin resistance being universally beneficial or universally primary.

Inflammation can connect these levels rather than compete with an energetic explanation. It can initiate stress, execute defense, support repair, and alter signals controlling fuel use and behavior. Hypothalamic inflammatory signaling disrupted insulin/leptin regulation in mouse overnutrition models, whereas related signaling promoted illness-associated anorexia in mouse challenge models ^{[4][5]}. Our synthesis proposes that such defensive regulation can change the conditions for restoration. Whether it protects, prolongs a limitation, or increases feeding depends on the affected cells and context—not simply on the presence of inflammation.

Several conceptual frameworks already illuminate recovery and multiscale vulnerability. Starting bioenergetic capacity and tissue demand help explain why the same challenge may affect tissues differently ^[6]. Healing can be understood as a transition among metabolic and signaling states, rather than simply the disappearance of an insult ^[7]. Competition among vital, stress, and maintenance work makes the timing of restoration important ^[8], while Exposure-Related Malnutrition asks why adequate intake may still leave recovery conditional ^[9]. Tippirote and Hoonkaew's bioenergetic-impedance framework connects residual constraints, buffering, and network effects, and proposes sequential challenges with independently measured limitations ^[10].

Building on these overlapping frameworks, we follow what must be restored between challenges and how an unfinished process could impair a tissue's service to the wider system. The practical contribution is to connect material replacement, processing capacity, and protective regulation to experiments that

distinguish a lower current burden from restored capacity for later work. KHK provides one worked example.

What recovery must restore

A restriction that contains present stress is not necessarily evidence that capacity has been restored. Nor must impaired metabolism mean low expenditure: higher resting expenditure was reported in mitochondrial-disease cohorts, with separate high-expenditure findings in patient-derived fibroblasts and experimentally perturbed healthy-donor fibroblasts ^[11]. Restricted entry, inefficient processing, and costly compensation therefore raise different recovery questions. Simply measuring available fuel or total expenditure will not distinguish them.

A *fragile cell*, as used here, has less margin for a later demand because some part of its capacity remains limited. That limitation must be measured separately from the poor performance it is meant to explain. Possibilities include a depleted molecular pool, impaired production under demand, a maintained defensive restriction, structural injury, or inadequate support from nearby cells. A normal resting ATP concentration would not rule these out. Conversely, a slowly recovering measurement is not automatically the cause of poor function. After ischemia in canine heart, selected mitochondrial respiratory functions recovered before mitochondrial adenine nucleotide content; the investigators did not attribute early contractile dysfunction to depressed mitochondrial respiration ^[12]. The practical question is which unfinished recovery process limits the work that matters next.

Some consequences of an earlier challenge can outlast improvement in the initiating conditions. After transplant-associated intestinal immune injury in mice, stem-cell organoid impairment persisted through passage and transfer and remained after measured inflammation was attenuated. The study linked altered oxidative phosphorylation, succinate, and DNA methylation to the injured state ^[13]. This makes persistent loss of regenerative competence a concrete recovery problem, while leaving open whether the proposed metabolic–epigenetic chain maintains all of that loss.

Timing can also change the response to another insult. In juvenile rats, a second mild brain injury during depressed regional glucose utilization caused a deeper and longer metabolic disturbance than an injury delivered after a longer interval ^[14]. Because several biological states changed with the interval, glucose utilization alone cannot be assigned the causal role. Together, these examples motivate measuring what remains altered between challenges, rather than treating elapsed time as proof of recovery.

Prior stress can also improve later performance. Delayed ischemic preconditioning in rats improved postanoxic respiratory recovery in mitochondria isolated from their hearts ^[15]. Recovery can therefore leave adaptive gains as well as residual burdens. To predict which will dominate, the framework must identify both before observing the next outcome. Repeated challenge is not inherently wear, and a changed baseline is not inherently damage.

A stronger possibility is that an unfinished restorative process helps keep a defensive response active. Mitochondrial condition can influence defense without a simple shortage of ATP: mitochondrial DNA stress can prime antiviral signaling without a drastic change in measured oxygen consumption, and a separate stress relay through OMA1, DELE1, and HRI alters translation of the stress-response regulator ATF4 ^{[16][17]}. These findings establish ways for mitochondrial stress to change regulation. They do not determine whether the resulting response accelerates restoration or interferes with it.

Consider mitochondrial machinery that remains impaired after an insult. Replacing its proteins and membranes must proceed while the cell continues ordinary and defensive work. We propose that, where a defensive cost or restriction limits that replacement, the unrepaired machinery could continue to elicit the response that delays its repair. The missing causal step is the return influence: defense would have to impede the particular restoration that could remove its stimulus. That influence remains unproven and requires a test of both directions. In other settings, defense may promote repair, an insult may still be active, injury may be fixed, or regulation may persist for reasons independent of the energetic limitation. These alternatives lead to different interventions and must remain distinguishable.

KHK as a test case for restoration

We use ketohexokinase (KHK)-dependent fructose metabolism because it makes a central paradox experimentally accessible: fuel abundance need not mean restored capacity. Repeated KHK-dependent metabolism of dietary and endogenously generated fructose has been proposed as a contributor to obesity and related metabolic dysfunction in modern dietary environments ^[18]. It offers a recurring processing demand, measurable material costs, and possible machinery and inflammatory consequences within a pathway that can be selectively reduced. The experiment follows directly: establish a deficit, lower verified KHK flux during recovery, and test whether capacity for a later demand improves while other burdens remain comparable. KHK's first reaction spends ATP to phosphorylate fructose; mouse loading experiments showed falls in inorganic phosphate and ATP ^[19]. In a human subgroup with metabolic dysfunction-associated steatotic liver disease, KHK inhibition prevented the transient hepatic

inorganic-phosphate fall after oral fructose [20]. This shows that the initial processing cost can be changed; it does not establish chronic depletion.

Recovery first requires distinguishing recharging retained molecules from replacing lost material. Interconversion among ATP, ADP, and AMP preserves the adenylate pool. Under intense experimental fructose loading, however, AMP deamination to IMP moves material outside it [19]; perfused-liver studies found purine release and incomplete nucleotide recovery during observation [21][22]. Salvage and synthesis may replenish the pool; simply rephosphorylating its remaining molecules does not. This gives restoration a measurable target, while a persistent pool deficit after ordinary human intake remains hypothetical. The target matters only if its incomplete recovery limits later work.

The same logic extends from materials to machinery. Cell studies connect KHK-dependent metabolism with oxidants and inflammatory signaling, and urate with mitochondrial changes; mouse studies show altered mitochondrial morphology and fatty-acid-handling proteins after hepatic KHK silencing [23][24][25]. Supplied urate also promoted lipid accumulation despite KHK silencing in the cited cell model [24]. These responses do not establish lasting damage. Xanthine-oxidoreductase inhibition changes both urate and oxidants, complicating causal attribution; changed morphology proves neither harmful fission nor deficient ATP production. Fission may support quality control. The decisive question is whether a functional limitation remains after the burden subsides, and whether renewing the machinery removes it.

A burden must also be located, not inferred from intake. Intestinal KHK-C deletion increased hepatic fructose spillover and steatosis in one mouse protocol, whereas another intestine-specific deletion study found benefits [26][27]. Delivery rate and intestinal processing capacity therefore help determine which cells face the demand. KHK-C is concentrated in liver, kidney, and small intestine, whereas KHK-A is more broadly expressed [28][29]. Expression is not flux, and flux is not injury. The framework asks where processing competes with cellular work and renewal—not simply where an enzyme is present or how much fructose was consumed.

KHK also lets us separate the origin of an injury from a burden that might hinder its recovery. Dietary fructose and fructose generated through the polyol pathway converge on KHK, as illustrated by defined glucose and high-salt mouse models [30][31]. Reducing verified KHK flux could therefore test whether relieving a recurring demand helps restore capacity after another insult. It need not identify KHK as the original cause, and it does not establish that inhibition or dietary change achieves restoration.

That distinction determines what counts as success. Delayed hepatic KHK knockdown improved selected metabolic outcomes during continued high-fat/fructose feeding in mice, but not measured hepatic inflammation [32]. Such improvement does not yet distinguish preventing further disturbance from repairing an existing deficit or establish durable challenge tolerance. The fructose-survival hypothesis offers an adaptive interpretation of fructose-linked responses [18]; here, the further question is whether protection leaves restorative work unfinished. Proposed connections to insulin regulation and appetite likewise require their own evidence. KHK earns its place here as a tractable test of the larger argument: does relieving an identified burden restore the capacity for later work?

From fragile cell to fragile tissue

A limited cell does not automatically make a limited tissue. Neighboring cells may take on additional work, and a tissue may have enough reserve to maintain its output. A *fragile tissue* emerges when this buffering can no longer preserve a service under demand. By service, we mean the work on which the rest of the tissue or body depends, such as maintaining a barrier, supplying blood, or supporting neurons. The location and function of affected cells can matter as much as their number. A small group with a critical supporting role may create a greater functional problem than a larger group whose work can readily be shared.

Experimental mosaics illustrate why compensation must be part of the explanation. In mice with respiratory-chain-deficient and intact neurons, intact cells buffered some consequences, while trans-neuronal degeneration also occurred. During fetal heart development, healthy cardiac cells compensated for deficient cells [33][34]. These genetic and developmental models are precedents for tissue buffering and its limits, not evidence of an acquired mosaic of KHK-weakened cells. They show why a cellular measurement must be connected to the tissue's organization and output before a tissue-level consequence can be inferred.

Repeated burdens could erode that margin through accumulating unrepaired damage, persistent loss of material needed for later work, or altered functional organization. We use *wear* for such consequences, rather than for any abnormal marker. Burdens need not amplify one another to cross a tissue threshold: even additive losses could exhaust the capacity that previously preserved function. Conversely, adaptive changes could strengthen buffering or remove a limitation. The progression from fragile cells to fragile tissue therefore depends on what has been lost, what has been gained, and how much compensating capacity remains when demand rises.

From fragile tissue to fragile system

Organs also depend on one another's services. A barrier defect may change what other tissues are exposed to; reduced vascular supply can limit a recipient's work; a circulating signal can change another organ's regulation. These routes make it possible for a local problem to alter conditions elsewhere without requiring the same cellular defect in every organ. In defined chronic-kidney-disease models, FGF23–FGFR4 signaling contributes to cardiac metabolic and structural remodeling ^{[35][36]}. Hepatic selenoprotein P provides another route, affecting insulin action in experimental recipient systems ^[37]. Each example supplies a particular signaling connection, rather than a general inference from two organs being abnormal at the same time.

A *fragile system* could arise when such a connection propagates a local deficit, or when several independently limited tissues cannot meet the same whole-organism demand. Propagation in one direction is enough for an effect beyond the source tissue. A self-maintaining cross-organ loop would require the additional demonstration that the recipient feeds back to sustain the source problem. This is the system-level counterpart of the cellular return influence: it is a further causal claim, not something established merely by connected physiology.

Inflammation and insulin regulation need not occupy the same position in every case. Inflammation could initiate a challenge, remain an ongoing input, or participate in repair; altered insulin action could change fuel entry or redistribute a burden. Their relationship must be established in the system being studied. In a male-mouse high-fructose model, whole-body KHK loss prevented a joint adipose inflammatory and insulin-resistance phenotype, without ordering those changes or isolating a tissue-specific mediator ^[38]. In another mouse diet model, hepatic inflammatory and fibrogenesis markers increased without a significant loss of insulin-stimulated hepatic Akt signaling at the measured time ^[39]. The examples allow both coupling and separation; they cannot be reduced to interchangeable signs of one energy deficit.

The same discipline applies to shared disease outcomes. If several outcomes arise partly from one upstream limitation, correcting it could potentially improve more than one of them. That possibility is the reason to trace the progression beyond the cell. It requires a route from the limitation to each outcome, while allowing inherited capacity, toxins, ongoing infection, oxygen delivery, and calorie balance to contribute at different points. An energetic explanation is useful where a measured processing,

material, or allocation constraint explains impaired work better than alternatives; its relevance in one pathway does not make it a universal cause.

Table 1 brings together the complementary accounts and the explanatory relationships proposed by the synthesis.

Complementary account	Explanatory question	Contribution to the unified sequence	Apparent contradiction clarified
Caloric accounting	How much energy enters, is stored, and is expended?	Constrains the whole-organism budget; regulated appetite and expenditure can also feed back on local burdens.	Abundant stores need not suppress feeding if the signals governing intake remain altered; energy balance still holds.
Insulin-mediated substrate distribution	Where are substrates delivered and admitted?	Locates regulated entry and redistribution; restricted uptake can be defensive in particular experimental settings [3].	Restricting entry may contain local stress while worsening whole-body fuel regulation; available substrate and usable capacity are different.
Inflammatory and stress signaling	How does defense change metabolism, fuel regulation, and behavior?	Can initiate a burden, coordinate defense or repair, or help maintain altered conditions; its role depends on tissue and stage.	A protective response can coexist with impaired function; inflammation need not have one cause or produce one appetite response.
Bioenergetic capacity and tissue demand (Wallace [6])	How do starting capacity and tissue requirements shape vulnerability?	Supplies initial conditions and tissue-specific thresholds.	The same exposure can leave different tissues with different margins because their starting capacities and tasks differ.
Healing-state transitions (Naviaux [7])	How do metabolic and signaling states change during defense and healing?	Supplies a dynamic account of protective and restorative states.	Survival and disappearance of the initiating insult do not by themselves establish that restorative work is complete.
Energy allocation among competing work (Behnke et al. [8])	How do vital, stress, and maintenance demands compete?	Identifies a possible trade-off between present work and renewal.	High expenditure can coexist with reduced specialized function when defense and compensation consume resources.
Exposure-Related Malnutrition	Why can recovery remain conditional	Centers the distinction between responding to	Adequate intake can coexist with incomplete recovery when

Complementary account	Explanatory question	Contribution to the unified sequence	Apparent contradiction clarified
(Tippairote et al. ^[9])	despite apparently adequate intake?	exposure and completing recovery.	processing, repair, or other recovery conditions remain limiting.
Fructose-survival hypothesis (Johnson et al. ^[18])	Could fructose-linked responses serve an adaptive program?	Offers an interpretation of one initiating route, distinct from established KHK biochemistry.	A fuel can also impose a processing burden; an adaptive interpretation does not establish lasting depletion or make KHK the universal origin.

Table 1. Complementary accounts and their causal roles in the unified hypothesis

Table note. The listed roles are selective and substantially overlapping, not exhaustive accounts of these frameworks. These accounts describe potentially connected levels, not mutually exclusive causes. The final column states explanatory relationships proposed by the synthesis, not demonstrations of the complete sequence. The framework does not require a universal ATP deficit, adaptive insulin resistance in every setting, or inflammation downstream of energetic depletion. KHK, ketohexokinase.

Tests of the transitions

Three comparisons can test the proposed progression. Each should define the physiological function at issue, the size of a meaningful change, the precision needed to detect it, and the conditions under which the proposed limitation would be expected to matter.

1. Separate restoration from marker change

After an initial insult has produced a documented deficit, reduce the insult and follow recovery serially. Measure the suspected material or processing limitation separately from resting markers and from performance under a later, unrelated demand. This timing distinguishes preventing the original deficit from correcting a limitation that is already present. Current exposure and other demands must be comparable, and any residual intervention effect during the later challenge must be accounted for. A

marker returning to normal is informative, but restoration requires the predicted improvement in function.

A prospective example could adapt the primary human proximal-tubule cytokine model, where respiratory suppression—not adenylate-pool depletion—was demonstrated [1]. After transient $\text{TNF-}\alpha$ exposure and washout, pilot work must establish a residual adenylate-pool deficit, measurable KHK flux, and reduced but measurable albumin uptake [40]. During recovery only, compare KHK inhibition with vehicle under matched fructose exposure, alongside uninjured controls. Track adenylates serially and ATP production under demand; verify flux reduction. After inhibitor washout, measure uptake during a short, pilot-validated noninjurious labeled-albumin pulse. Improvement from the documented deficit in both pool size and uptake supports net restoration; improved uptake without pool correction points to another route. Pool correction without functional benefit weakens the proposed limitation when prespecified co-limitations, including receptor loss and viability, are addressed. Normal resting ATP is neither required nor proof of repair.

Because catalytically inactive KHK-C altered stress signaling in a cell-overexpression experiment [32], catalytic inhibition and KHK protein depletion should not be assumed equivalent. An orthogonal correction of the proposed limitation, independent of KHK manipulation, would strengthen the mediation test.

2. Test what changes between challenges

Vary the recovery interval and ask what changes with it. At comparable current exposure, later vulnerability should follow the proposed residual limitation and change when that limitation is selectively corrected. If the prior challenge itself improves later performance at comparable current exposure, that supports an adaptive branch. Measuring the intervening state is essential: a longer interval changes many processes and does not by itself identify the one responsible.

A proposed maintenance loop requires two tests. Relieving the limitation should change the defense it is thought to sustain; removing the defense's particular interference should improve restoration. Failure of either connection weakens that loop without erasing a remaining one-way effect. The model should predict a change in the duration of vulnerability only when it assigns that duration to the process being altered.

3. Trace tissue and cross-organ effects

At each step beyond the cell, identify the service or signal that carries the effect. Selectively restoring the implicated cells or their service should improve the predicted organ function under conditions where other limitations do not mask the change. For a cross-organ route, altering the source or recipient side of the pathway should change the predicted recipient function. A reciprocal loop requires a separate return effect.

If several tissues are independently vulnerable, measure them during the same organismal demand and selectively correct their proposed local limitations. Co-occurring abnormalities alone cannot distinguish parallel vulnerability from propagation. Each test should state whether a factor is proposed to be necessary, sufficient, or contributory and identify plausible co-limitations before interpreting an unsuccessful rescue.

A Unified View of Metabolic Dysfunction

The central proposal is that energetic burdens can influence not only how much work cells perform, but which work they preserve and which restorative work remains unfinished. Whole-body calorie accounting and insulin-mediated fuel distribution describe essential parts of this process. Following recovery adds the question of whether cells regain the capacity to maintain, repair, and coordinate their work before another demand arrives. Tissue buffering and cross-organ connections determine how far a local limitation matters. KHK provides one tractable route through this larger problem, not its universal explanation.

If a shared barrier to restoration contributes to several disease outcomes, identifying and correcting it could redirect research from tracking those outcomes separately toward testing a common cause of impaired function. That is a therapeutic possibility to investigate, not evidence of an established treatment or superiority over existing approaches. The value of the framework lies in making the alternatives testable: where does protection lead to recovery, where does a limitation remain, and when does correcting it improve the work of the cell, tissue, or system?

Notes

An earlier related hypothesis was posted by Christopher Ryan Mearns and Paul Gross as *The KHK–Polyol Axis as a Convergent Energetic Bottleneck in Chronic Disease Persistence* (Qeios, Preprint v1, 16 February 2026;

<https://doi.org/10.32388/R2NFG9>). The present article develops a broader conditional framework centered on conservation, restoration, and multiscale fragility. The earlier preprint is disclosed as related prior work, not as independent empirical evidence for the sequence proposed here.

Statements and declarations

Funding

This work was undertaken as an independent personal project and was funded by the author.

Potential Competing Interests

Christopher Ryan Mearns is the founder and an owner of LIV3 Health, which develops nutritional protocols and dietary supplements, including SugarShield. This commercial interest is relevant to the subject matter of the manuscript. No commercial product is evaluated in this article, and it does not establish the clinical efficacy or human KHK-inhibitory activity of any LIV3 Health product.

Ethics

This article is a conceptual synthesis of published literature. It reports no new human-participant research, animal experiments, or individual clinical data. Ethics approval and participant consent are not applicable to the work reported.

Data Availability

The article synthesizes evidence from the cited publications and reports no new primary experimental or clinical dataset.

Author Contributions

Christopher Ryan Mearns conceived and developed the hypothesis, directed the literature synthesis, and guided the manuscript's interpretation and revision. The author is responsible for the accuracy and integrity of the work.

Use of Generative AI

ChatGPT and Codex (OpenAI) assisted with literature research and manuscript drafting and revision under the author's direction. The author developed the hypothesis and takes responsibility for the

interpretation, accuracy and final content.

References

1. ^a ^bTran M, et al (2011). "PGC-1 α Promotes Recovery After Acute Kidney Injury During Systemic Inflammation in Mice." *J Clin Invest*. **121**(10):4003–4014. doi:[10.1172/JCI58662](https://doi.org/10.1172/JCI58662).
2. ^ΔMinokoshi Y, et al (2004). "AMP-Kinase Regulates Food Intake by Responding to Hormonal and Nutrient Signals in the Hypothalamus." *Nature*. **428**(6982):569–574. doi:[10.1038/nature02440](https://doi.org/10.1038/nature02440).
3. ^a ^bHoehn KL, et al (2009). "Insulin Resistance Is a Cellular Antioxidant Defense Mechanism." *Proc Natl Acad Sci U S A*. **106**(42):17787–17792. doi:[10.1073/pnas.0902380106](https://doi.org/10.1073/pnas.0902380106).
4. ^ΔZhang X, et al (2008). "Hypothalamic IKK β /NF- κ B and ER Stress Link Overnutrition to Energy Imbalance and Obesity." *Cell*. **135**(1):61–73. doi:[10.1016/j.cell.2008.07.043](https://doi.org/10.1016/j.cell.2008.07.043).
5. ^ΔJang PG, et al (2010). "NF- κ B Activation in Hypothalamic Pro-Opiomelanocortin Neurons Is Essential in Illness- and Leptin-Induced Anorexia." *J Biol Chem*. **285**(13):9706–9715. doi:[10.1074/jbc.M109.070706](https://doi.org/10.1074/jbc.M109.070706).
6. ^a ^bWallace DC (2011). "Bioenergetic Origins of Complexity and Disease." *Cold Spring Harb Symp Quant Biol*. **76**:1–16. doi:[10.1101/sqb.2011.76.010462](https://doi.org/10.1101/sqb.2011.76.010462).
7. ^a ^bNaviaux RK (2023). "Mitochondrial and Metabolic Features of Salugenesis and the Healing Cycle." *Mitochondrion*. **70**:131–163. doi:[10.1016/j.mito.2023.04.003](https://doi.org/10.1016/j.mito.2023.04.003).
8. ^a ^bBehnke A, et al (2026). "Energy Constraint on Human Health." *Trends Endocrinol Metab*. **37**(10):927–947. doi:[10.1016/j.tem.2026.02.010](https://doi.org/10.1016/j.tem.2026.02.010).
9. ^a ^bTippairote T, et al (2026). "Stress Is Inevitable; Recovery Is Conditional: Bioenergetic Limits of Resilience in Aging and Disease." *Biogerontology*. **27**:96. doi:[10.1007/s10522-026-10445-w](https://doi.org/10.1007/s10522-026-10445-w).
10. ^ΔTippairote T, Hoonkaew P (2026). "Bioenergetic Impedance: A Network Physiology Framework for Stress Adaptation, Maladaptation, and Recovery." *Front Netw Physiol*. **6**:1967461. doi:[10.3389/fnetp.2026.1967461](https://doi.org/10.3389/fnetp.2026.1967461).
11. ^ΔSturm G, et al (2023). "OxPhos Defects Cause Hypermetabolism and Reduce Lifespan in Cells and in Patients With Mitochondrial Diseases." *Commun Biol*. **6**(1):22. doi:[10.1038/s42003-022-04303-x](https://doi.org/10.1038/s42003-022-04303-x).
12. ^ΔAsimakis GK, et al (1992). "Postischemic Recovery of Mitochondrial Adenine Nucleotides in the Heart." *Circulation*. **85**(6):2212–2220. doi:[10.1161/01.CIR.85.6.2212](https://doi.org/10.1161/01.CIR.85.6.2212).
13. ^ΔZhao D, et al (2024). "Inflammation-Induced Epigenetic Imprinting Regulates Intestinal Stem Cells." *Cell Stem Cell*. **31**(10):1447–1464.e6. doi:[10.1016/j.stem.2024.08.006](https://doi.org/10.1016/j.stem.2024.08.006).

14. [△]Prins ML, et al (2013). "Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability." *J Neurotrauma*. **30**(1):30–38. doi:[10.1089/neu.2012.2399](https://doi.org/10.1089/neu.2012.2399).
15. [△]McLeod CJ, et al (2004). "Delayed Ischemic Preconditioning Activates Nuclear-Encoded Electron-Transfer-Chain Gene Expression in Parallel With Enhanced Postanoxic Mitochondrial Respiratory Recovery." *Circulation*. **110**(5):534–539. doi:[10.1161/01.CIR.0000136997.53612.6C](https://doi.org/10.1161/01.CIR.0000136997.53612.6C).
16. [△]West AP, et al (2015). "Mitochondrial DNA Stress Primes the Antiviral Innate Immune Response." *Nature*. **520**(7548):553–557. doi:[10.1038/nature14156](https://doi.org/10.1038/nature14156).
17. [△]Guo X, et al (2020). "Mitochondrial Stress Is Relayed to the Cytosol by an OMA1–DELE1–HRI Pathway." *Nature*. **579**(7799):427–432. doi:[10.1038/s41586-020-2078-2](https://doi.org/10.1038/s41586-020-2078-2).
18. [△][♢]Johnson RJ, et al (2023). "The Fructose Survival Hypothesis for Obesity." *Philos Trans R Soc Lond B Biol Sci*. **378**(1885):20220230. doi:[10.1098/rstb.2022.0230](https://doi.org/10.1098/rstb.2022.0230).
19. [△][♢]van den Berghe G, et al (1977). "The Mechanism of Adenosine Triphosphate Depletion in the Liver After a Load of Fructose. A Kinetic Study of Liver Adenylate Deaminase." *Biochem J*. **162**(3):601–609. doi:[10.1042/bj1620601](https://doi.org/10.1042/bj1620601).
20. [△]Koene EJC, et al (2025). "Safety and Efficacy of Pharmacological Inhibition of Ketohexokinase in Hereditary Fructose Intolerance." *J Clin Invest*. **135**(6):e187376. doi:[10.1172/JCI187376](https://doi.org/10.1172/JCI187376).
21. [△]Nishi T, et al (1989). "The Effect of Fructose on the Cellular Content of Adenine Nucleotides in the Perfused Rat Liver." *Jpn J Surg*. **19**(3):351–357. doi:[10.1007/BF02471412](https://doi.org/10.1007/BF02471412).
22. [△]Thoma WJ, Uğurbil K (1989). "Effect of Adenine on Liver Nucleotide After Fructose Loading by 31P-NMR." *Am J Physiol*. **256**(6 Pt 1):G949–G956. doi:[10.1152/ajpgi.1989.256.6.G949](https://doi.org/10.1152/ajpgi.1989.256.6.G949).
23. [△]Cirillo P, et al (2009). "Ketohexokinase-Dependent Metabolism of Fructose Induces Proinflammatory Mediators in Proximal Tubular Cells." *J Am Soc Nephrol*. **20**(3):545–553. doi:[10.1681/ASN.2008060576](https://doi.org/10.1681/ASN.2008060576).
24. [△][♢]Lanaspa MA, et al (2012). "Uric Acid Induces Hepatic Steatosis by Generation of Mitochondrial Oxidative Stress: Potential Role in Fructose-Dependent and -Independent Fatty Liver." *J Biol Chem*. **287**(48):40732–40744. doi:[10.1074/jbc.M112.399899](https://doi.org/10.1074/jbc.M112.399899).
25. [△]Softic S, et al (2019). "Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-Translational Modifications of Mitochondrial Proteins." *Cell Metab*. **30**(4):735–753.e4. doi:[10.1016/j.cmet.2019.09.003](https://doi.org/10.1016/j.cmet.2019.09.003).
26. [△]Jang C, et al (2020). "The Small Intestine Shields the Liver From Fructose-Induced Steatosis." *Nat Metab*. **2**:586–593. doi:[10.1038/s42255-020-0222-9](https://doi.org/10.1038/s42255-020-0222-9).

27. [△]Song S, et al (2026). "Intestinal-Specific Ketohexokinase Deficiency Ameliorates High Fructose-Induced Metabolic Dysfunction Across the Intestinal-Liver-Kidney Axis in Mice." *J Nutr Biochem.* **157**:110453. doi:[10.1016/j.jnutbio.2026.110453](https://doi.org/10.1016/j.jnutbio.2026.110453).
28. [△]Diggle CP, et al (2009). "Ketohexokinase: Expression and Localization of the Principal Fructose-Metabolizing Enzyme." *J Histochem Cytochem.* **57**(8):763–774. doi:[10.1369/jhc.2009.953190](https://doi.org/10.1369/jhc.2009.953190).
29. [△]Diggle CP, et al (2010). "Both Isoforms of Ketohexokinase Are Dispensable for Normal Growth and Development." *Physiol Genomics.* **42A**(4):235–243. doi:[10.1152/physiolgenomics.00128.2010](https://doi.org/10.1152/physiolgenomics.00128.2010).
30. [△]Lanaspa MA, et al (2013). "Endogenous Fructose Production and Metabolism in the Liver Contributes to the Development of Metabolic Syndrome." *Nat Commun.* **4**:2434. doi:[10.1038/ncomms3434](https://doi.org/10.1038/ncomms3434).
31. [△]Lanaspa MA, et al (2018). "High Salt Intake Causes Leptin Resistance and Obesity in Mice by Stimulating Endogenous Fructose Production and Metabolism." *Proc Natl Acad Sci U S A.* **115**(12):3138–3143. doi:[10.1073/pnas.1713837115](https://doi.org/10.1073/pnas.1713837115).
32. ^{a, b}Park SH, et al (2023). "Fructose-Induced KHK-C Can Increase ER Stress Independent of Its Effect on Lipogenesis to Drive Liver Disease in Diet-Induced and Genetic Models of NAFLD." *Metabolism.* **145**:155591. doi:[10.1016/j.metabol.2023.155591](https://doi.org/10.1016/j.metabol.2023.155591).
33. [△]Dufour E, et al (2008). "Age-Associated Mosaic Respiratory Chain Deficiency Causes Trans-Neuronal Degeneration." *Hum Mol Genet.* **17**(10):1418–1426. doi:[10.1093/hmg/ddn030](https://doi.org/10.1093/hmg/ddn030).
34. [△]Drenckhahn JD, et al (2008). "Compensatory Growth of Healthy Cardiac Cells in the Presence of Diseased Cells Restores Tissue Homeostasis During Heart Development." *Dev Cell.* **15**(4):521–533. doi:[10.1016/j.devcel.2008.09.005](https://doi.org/10.1016/j.devcel.2008.09.005).
35. [△]Fuchs MAA, et al (2025). "Fibroblast Growth Factor 23 and Fibroblast Growth Factor Receptor 4 Promote Cardiac Metabolic Remodeling in Chronic Kidney Disease." *Kidney Int.* **107**(5):852–868. doi:[10.1016/j.kint.2025.01.024](https://doi.org/10.1016/j.kint.2025.01.024).
36. [△]Grabner A, et al (2017). "FGF23/FGFR4-Mediated Left Ventricular Hypertrophy Is Reversible." *Sci Rep.* **7**(1):1993. doi:[10.1038/s41598-017-02068-6](https://doi.org/10.1038/s41598-017-02068-6).
37. [△]Misu H, et al (2010). "A Liver-Derived Secretory Protein, Selenoprotein P, Causes Insulin Resistance." *Cell Metab.* **12**(5):483–495. doi:[10.1016/j.cmet.2010.09.015](https://doi.org/10.1016/j.cmet.2010.09.015).
38. [△]Marek G, et al (2015). "Adiponectin Resistance and Proinflammatory Changes in the Visceral Adipose Tissue Induced by Fructose Consumption via Ketohexokinase-Dependent Pathway." *Diabetes.* **64**(2):508–518. doi:[10.2337/db14-0411](https://doi.org/10.2337/db14-0411).

39. ^ΔSangüesa G, et al (2017). "The Addition of Liquid Fructose to a Western-Type Diet in LDL-R^{-/-} Mice Induces Liver Inflammation and Fibrogenesis Markers Without Disrupting Insulin Receptor Signalling After an Insulin Challenge." *Nutrients*. **9**(3):278. doi:[10.3390/nu9030278](https://doi.org/10.3390/nu9030278).
40. ^ΔTang S, et al (2003). "Albumin Stimulates Interleukin-8 Expression in Proximal Tubular Epithelial Cells in Vitro and in Vivo." *J Clin Invest*. **111**(4):515–527. doi:[10.1172/JCI16079](https://doi.org/10.1172/JCI16079).

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: Christopher Ryan Mearns is the founder and an owner of LIV3 Health, which develops nutritional protocols and dietary supplements, including SugarShield. This commercial interest is relevant to the subject matter of the manuscript. No commercial product is evaluated in this article, and it does not establish the clinical efficacy or human KHK-inhibitory activity of any LIV3 Health product.