Review Article

Ketohexokinase-Dependent Fructose Metabolism as a Potential Upstream Amplifier of Mast-Cell Activation – A Hypothesis Linking Endogenous Fructose Production, Tissue Danger Signaling, and Impaired Recovery

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1. Independent researcher

Why do mast cells remain unusually responsive between episodes in some people with idiopathic mast-cell activation syndrome (MCAS)? We propose that fructose metabolism in surrounding tissue may help sustain this state. Ketohexokinase (KHK) begins fructose metabolism by spending ATP, a molecule that supplies energy for cellular work. If this initial processing outruns the cell's capacity to handle the products and replenish ATP, it can disturb energy balance and promote oxidative stress. Fructose may come from the diet or be made within the body through the polyol pathway. We hypothesize that KHK-dependent tissue stress increases extracellular signals that heighten mast-cell responses. Mast-cell mediators could then reinforce tissue stress and delay recovery. This mechanism does not require mast cells themselves to lack ATP. Experimental studies support individual steps, but no study reviewed here establishes the complete connection in MCAS. We prioritize signals from neighboring tissue; direct fructose metabolism within mast cells requires separate validation. Proposed experiments would track fructose metabolism, transfer fluid from source tissue to human mast cells, and interrupt KHK separately in each cell population. In models showing both KHK activity and heightened mast-cell responsiveness, we predict that source-tissue KHK interruption will reduce this amplification and shorten recovery without impairing mast-cell function. Failure despite verified KHK inhibition over a predefined recovery interval would weaken the tested mechanism. Luteolin offers an additional probe because it independently inhibits mast-cell activity and shows

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experimental KHK inhibition; a response cannot identify which action matters. Clinical relevance requires validation in rigorously characterized MCAS populations.

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1. Why might mast cells fail to settle?

What keeps mast cells unusually responsive after an episode has passed? One possibility is that surrounding tissue continues to supply signals that make the next response easier to trigger or larger. We propose that fructose metabolism through ketohexokinase (KHK) could contribute to this continuing input. Stressed tissue could stimulate mast cells that still have ample energy to respond. Their inflammatory products could then add to the tissue's burden, creating a cycle that delays recovery.

The clinical question concerns idiopathic mast-cell activation syndrome (MCAS). Mast cells release substances such as histamine that contribute to inflammatory and allergic responses. Established MCAS criteria combine recurrent compatible systemic episodes, objectively increased mast-cell mediators, and response to treatment directed at those mediators. Clinicians diagnose idiopathic MCAS when they cannot identify an abnormal mast-cell clone or a secondary cause, such as allergy. Non-clonal MCAS includes both idiopathic and secondary disease [1]. The proposed metabolic contribution would modify responsiveness within this clinical framework.

Earlier work already proposes energetic instability in MCAS [2], and a 2013 patent connects KHK inhibition with intestinal permeability and food allergy [3]. Our contribution is a specific question: can KHK-active tissue send signals that heighten mast-cell responses, and does interrupting that metabolic activity help the system recover?

We address this question through a targeted narrative review. The main searches extended through 8 November 2026, with a targeted pharmacokinetic check on 9 November. Sources identified through web searches, PubMed-indexed records, publisher and PMC pages, and citation following were selected for relevance to mechanism, counterevidence, or experimental design. Some findings were assessed at abstract level. This approach identifies evidence and testable gaps; it is not an exhaustive systematic review or a claim to priority, and source selection may introduce bias.

2. Recovery means more than a quiet cell

The Conserving Cell framework asks whether a cell has merely survived a challenge or rebuilt the resources needed for later work [4]. The related KHK–Polyol Axis hypothesis identifies fructose metabolism as one possible obstacle to that rebuilding [5]. It emphasizes disturbed ATP and phosphate balance. ATP supplies energy for cellular work; sufficiently high or repeated fructose processing can deplete the recyclable molecules used to rebuild it. These earlier preprints motivate the present question; they do not independently demonstrate a KHK mechanism in MCAS.

The key distinction is between the tissue generating stress and the mast cell responding to it. Cells lining the intestine, for example, could struggle to restore normal function while nearby mast cells maintain or increase their capacity to release inflammatory mediators. The framework's idea of conservation concerns how cells allocate resources between immediate demands and restoration. It does not require every cell to slow its metabolism.

Mast-cell biology makes this distinction necessary. Blocking glucose breakdown and ATP production reduces mast-cell responses to the inflammatory signal interleukin-33 (IL-33) [6]. A 2026 human study links MITF, a regulator of gene activity, to mitochondrial function and reports increased respiration—the oxygen use associated with metabolism—in mast cells from patients with food anaphylaxis [7]. A systematic review also identifies mitochondrial respiration, calcium regulation, and mitochondrial movement as parts of mast-cell activation and release of stored mediators, or degranulation [8]. Metabolic activity can support the response; a change in mitochondria does not automatically mean failure.

Experiments must therefore ask three questions: how much does a mast cell release at rest, how strongly does it respond to a challenge, and how does it recover afterward? ATP levels, extracellular signals, and responsiveness may recover at different rates. If ATP returns to normal while responses remain exaggerated, an ongoing ATP shortage cannot by itself explain the result. If release falls because cells are damaged or cannot secrete, the experiment has not shown recovery.

The proposed benefit of KHK interruption is to relieve a continuing tissue input while preserving appropriate mast-cell responses. Showing less secretion is only the first step. Showing recovery requires evidence that cells can perform normally when challenged again.

3. How fructose processing could create a burden

Fructose metabolism starts with an upfront energy cost. KHK uses ATP, a molecule that supplies energy for cellular work, to attach phosphate to fructose, producing fructose-1-phosphate. Later steps can help replenish that investment. But if the initial processing outruns the cell's ability to handle the products and restore its energy balance, available ATP and inorganic phosphate can fall. Breakdown of ATP's building blocks can also increase. The fructose-survival hypothesis interprets these changes as an adaptive response that may become costly with excessive or repeated activation [9]. The proposed problem is a mismatch between processing and replenishment, not an inevitable consequence of using fructose.

The fructose need not come directly from food. The body can convert glucose to sorbitol through aldose reductase, then sorbitol to fructose through sorbitol dehydrogenase. Together, these reactions form the polyol pathway. Experiments in glucose-fed mice demonstrate endogenous fructose production and KHK-dependent metabolic effects [10]. Whether ordinary changes in human blood glucose generate enough fructose near mast cells to affect their behavior remains unknown.

Human measurements establish exposure, but not the proposed local mechanism. In nine healthy volunteers, a dual-tracer study measured fasting plasma fructose of 17.9 ± 0.6 µM and estimated that 14.5% of ingested fructose reached systemic circulation over four hours [11]. Neither measurement shows how much fructose a particular tissue produces or processes through KHK. That processing rate, termed metabolic flux, depends on substrate delivery, transport, the version of KHK present, and downstream capacity. Detecting the enzyme alone does not establish flux or injury.

The polyol pathway also changes the cell's chemical balance before fructose reaches KHK. Aldose reductase consumes NADPH, which helps support antioxidant defenses; sorbitol dehydrogenase converts NAD+ to NADH. Experimental work links these upstream reactions to oxidative stress, an imbalance between reactive molecules and the cell's defenses [12]. Researchers must separate their contribution from KHK's. Measurements of NADPH/NADP+ and NADH/NAD+, together with selective interventions, can help. Blocking an upstream enzyme also reduces fructose supply, so an improvement alone would not identify which step caused the stress.

Kidney studies show that KHK can contribute to inflammatory activity. In human proximal tubular cells, KHK-dependent fructose metabolism increased reactive oxygen species and release of monocyte chemoattractant protein-1, an inflammatory signal [13]. Research on kidney injury caused by restricted

blood flow also links endogenous fructose metabolism to ATP depletion, oxidative stress, and injury [14]. These findings establish relevant components, but acute kidney injury cannot establish chronic signaling from otherwise viable intestinal tissue.

A closer immune example comes from primary human monocytes. Exposure to 50 μM fructose increased selected responses to a later bacterial stimulus, lipoteichoic acid; a KHK inhibitor reduced some of those responses [15]. An early ATP reduction was no longer detectable at later measurements. A separate human intake experiment also found increased responses in monocytes collected after a high fructose exposure. However, the cell experiments used glucose-free medium with serum and lacked genetic confirmation or isotope-verified flux. They support testing metabolic amplification, not a demonstrated mast-cell mechanism or lasting memory after fructose removal.

The crucial question is what connects these observations. High glucose, low oxygen, and osmotic stress can act through pathways other than fructose metabolism. If KHK drives the proposed effect, verified interruption of its activity should reduce it. Upstream chemical stress could persist despite KHK interruption. A damaged barrier could instead admit more allergen without changing mast-cell sensitivity. Measuring an inflammatory marker alone cannot distinguish these explanations.

4. Where would the mechanism operate?

4.1. Signals from neighboring tissue

The leading hypothesis starts outside the mast cell. The intestinal lining offers a useful first model because it processes dietary fructose and sits close to tissue-resident mast cells. Intestinal processing can limit how much fructose reaches the liver, while high-fructose models also link barrier deterioration to inflammation [16][17]. The intestine could therefore protect downstream organs while, under other conditions, experiencing local stress.

This dual role makes the location of KHK activity important. Genetic studies report different outcomes: protective intestinal KHK-C clearance, reduced sugar intake after deletion of both KHK versions, and improved barrier and metabolic outcomes in another intestinal deletion model [18][19][20]. These models differ in the enzyme versions targeted, fructose exposure, and actual sugar intake. Intestinal KHK interruption can change absorption, intake, and downstream delivery as well as local metabolism. Researchers must measure those changes rather than assume that inhibition is beneficial.

They must also distinguish greater exposure from greater responsiveness. A leakier barrier may let more allergen reach mast cells. A sensitizing tissue signal would instead produce a larger response to the same amount of trigger. This distinction allows a continuing local environment to explain heightened responsiveness without requiring permanent changes within mast cells.

Other tissues need their own evidence. Fructose metabolism in tumor endothelial cells can increase respiration and ATP [21], illustrating why KHK activity need not produce energy failure. Kidney findings likewise cannot locate a mechanism in the intestinal lining.

4.2. Fructose metabolism within mast cells

The second route places KHK inside mast cells themselves. It requires evidence that they encounter or make fructose and process enough of it to change their responses. KHK-A and KHK-C are different versions of the enzyme. The version present and its activity require measurement. Failure to find KHK-C would specifically weaken a mechanism requiring that version.

The direct route needs measurements of the relevant KHK version, protein, and fructose flux. RNA abundance alone would not establish these functional requirements. The tissue-mediated route does not require mast-cell KHK expression, so we prioritize it while keeping the direct question separate.

5. How tissue stress might reach mast cells

ATP has two relevant roles: it supplies energy inside cells and can act as a signal outside them. A fall in intracellular ATP does not establish an increase outside the cell. Researchers must measure release, breakdown, and the concentration that actually reaches mast-cell receptors.

Human mast cells can respond to extracellular ATP, but the response depends on dose and context. In cultured LAD2 mast cells, substantial degranulation through the ATP-sensing receptor P2X7 required millimolar ATP concentrations [22]. At 100 µM, ATP increased histamine release during stimulation through IgE, an antibody involved in allergic responses, without directly triggering release; this human lung mast-cell experiment favored P2Y receptors [23]. Prior IL-33 exposure also increased degranulation responses to 100 and 1000 µM ATP in primary human mast cells [24].

Conversely, ATP and ADP reduced selected cytokine responses in human cord-blood-derived mast cells [25]. ATP is therefore a candidate signal, not a uniformly activating one. Blocking P2X7 alone would

not test every ATP-dependent mechanism. No study reviewed here establishes the relevant local signal concentration in MCAS.

Mitochondrial material provides another candidate. Stimulated human LAD2 cells release mitochondrial components, including DNA and ATP, with inflammatory effects on themselves and other cells [26]. Mouse studies also link ATP–P2X7 signaling to mast-cell-dependent intestinal inflammation [27]. These findings support downstream parts of the hypothesis. They do not show that KHK-active tissue supplies the relevant signal. Researchers must also distinguish release by living cells from leakage after cell injury. Different mitochondrial components may act through different receptors.

A related feedback circuit shows how one cell population can amplify another. IL-33-stimulated mast cells activated platelets through signaling involving leukotriene C4 (LTC4); platelet-derived nucleotides then increased mast-cell output [28]. Mouse genetics identified key receptor requirements, with supporting human-cell and airway observations. This precedent makes a reciprocal circuit worth testing, but neither implicates KHK nor demonstrates impaired epithelial recovery. Platelets are also an alternative ATP source to consider where relevant.

Our proposed loop requires three connected effects: KHK-dependent tissue stress increases a signal; that signal heightens mast-cell output; mast-cell products then delay recovery of the originating tissue. The last step matters. Increased histamine alone does not demonstrate feedback, tissue damage, or continuing KHK activity. If heightened responsiveness persists after verified KHK interruption, researchers must allow a predefined recovery interval and investigate residual signals or an independently maintained process.

High-glucose studies reinforce the need for selective tests. Some human mast-cell-line and diabetic-mouse studies report increased inflammatory activity and mitochondrial stress [29][30]. Another mouse mast-cell study found little effect of elevated glucose on the functions tested, despite requiring glucose transport for optimal IgE responses [31]. Glucose exposure, cell state, and duration matter; none of these findings alone identifies KHK as the mediator.

6. Why luteolin belongs in the investigation

Luteolin has an independent mast-cell rationale. Cultured human mast-cell studies report reduced mediator release involving calcium and protein kinase C signaling [32]. Other experiments find inhibition through both IgE-dependent pathways and MRGPRX2, a receptor that can activate mast cells

independently of IgE [33]. A comparison with cromolyn found greater potency under the culture conditions tested [34], without establishing clinical superiority.

A 2026 consensus-2 review includes luteolin among flavonoid treatment options [35]. That review documents clinical consideration within one diagnostic tradition; it does not establish controlled efficacy in confirmed idiopathic MCAS or agreement across diagnostic frameworks. Reported improvement cannot identify a molecular target.

Luteolin's experimental KHK inhibition supplies a separate reason to study it. Kidney research reports an enzyme-assay IC50 of 11.2 μM—the concentration producing half-maximal inhibition—and protection in intravenously treated mice [14]. Biochemical inhibition of CD38, an enzyme involved in NAD metabolism, provides a secondary connection to the earlier energy framework [36]. These findings do not establish simultaneous inhibition after oral dosing. Whether oral luteolin can sustain enough active compound inside intestinal cells to inhibit KHK remains an open feasibility question. Concentration in the gut lumen does not establish intracellular exposure, and the enzyme-assay IC50 does not establish the concentration needed in living tissue.

The useful experiment compares luteolin with selective KHK interventions, including cells lacking KHK. If luteolin still acts after KHK loss, that residual effect supports other pharmacology. If luteolin helps but selective KHK interruption does not, its response would not validate the proposed mechanism. Complementary actions are possible; synergy requires a separate test. Experiments must distinguish the active parent compound from metabolites, verify non-toxic intracellular exposure, and control for assay interference.

7. Testing the tissue-to-mast-cell mechanism

The first experiment asks a simple question: does changing KHK activity in source tissue change how otherwise functional human mast cells respond? Here, source tissue means the cells proposed to generate the signal; recipient mast cells are those exposed to it. The steps below outline proposed tests of metabolic activity, signal transfer, recovery, and feedback; they are not completed experiments.

7.1. First, verify the metabolic activity

Researchers must establish that the chosen cells actually process fructose through KHK. Isotope tracing follows labeled fructose into fructose-1-phosphate or, for endogenous production, labeled glucose

through sorbitol and fructose. Time courses, enzyme-version measurements, and selective interventions distinguish metabolic flow from accumulation of a product. Measurements of ATP/phosphate balance, oxidative stress, mitochondrial function, and cell survival then characterize the disturbance. A direct mast-cell mechanism needs equivalent evidence within mast cells.

7.2. Next, test whether released signals increase responses

The proposed model pairs human intestinal organoid-derived monolayers with primary human progenitor-derived mast cells, followed by confirmation in intestinal mast cells. The monolayers form a polarized barrier with a gut-facing side and a tissue-facing side. Researchers would apply fructose to the gut-facing surface and collect fluid from the other side while monitoring barrier integrity. This collected fluid, or conditioned medium, tests what the source cells deliver to their surroundings. An independent pilot would fix relevant exposures and collection times from flux and viability measurements before testing mast-cell responses. Mixed-substrate conditions should test whether effects persist in the presence of physiologically relevant glucose.

The main comparison uses medium from untreated sources, fructose-exposed sources, and sources in which a selective inhibitor or genetic intervention interrupts KHK. Matched fluid without source cells and mast-cell-only controls account for residual sugars, inhibitor, pH, and osmolality. Intervening separately in source cells and mast cells locates the requirement. Agreement between pharmacological and genetic results, with restoration by active but not inactive KHK, would strengthen the case for catalytic activity. Continued drug effects after effective KHK loss would indicate other actions. Any candidate signal must survive collection and transfer for a negative result to test it meaningfully.

The primary outcome asks whether the same graded challenge produces more histamine release. After standardized IgE sensitization, researchers would measure the response across a predefined log anti-IgE concentration range and compare the area under that curve with matched control medium. Release would be expressed as a fraction of total histamine, released plus cell-associated, with condition-specific spontaneous release subtracted. Curves would not be scaled to their own maxima. Absolute release, maximal output, and viability remain separate measures. A larger area shows amplification; a lower activation threshold requires separate sensitivity analysis.

ATP would be the first candidate signal. Researchers would measure its concentration, test controlled degradation and receptor interventions, and ask whether the amount actually present explains the response. Receptor tests would follow an independent functional pilot and include controls for nucleotide

breakdown products and direct receptor effects. The predicted KHK-dependent result is less source signaling and less mast-cell amplification, with preserved survival and secretory capacity.

7.3. Then, ask whether the system recovers

Preventing a disturbance, suppressing secretion, and restoring function are different achievements. A recovery-only schedule would start intervention after a documented disturbance, with continuing source-cell KHK flux measured. At predefined intervals, researchers would test source medium in fresh mast-cell aliquots. The endpoint is the time until the recipient response-curve area returns within a predefined equivalence margin around matched-control values. This measures how long the source medium amplifies responses, not recovery within previously exposed mast cells; the latter requires separate washout and rechallenge experiments. Without continuing source flux, the schedule cannot test relief of an ongoing KHK burden.

To establish restored tissue capacity, researchers would remove the inhibitor and test a later standardized functional challenge under matched current exposure. To establish feedback, they would ask whether mast-cell products delay epithelial barrier recovery, with viability controls. Improved resting measurements alone would establish neither later capacity nor a return effect.

7.4. What results would weaken the hypothesis?

If verified source-cell KHK suppression fails to reduce heightened mast-cell responses meaningfully over a predefined interval, the tissue-mediated explanation weakens in that model. If validated assays with positive controls find no mast-cell fructose flux, the direct route weakens in that state. An increased response after KHK interruption would oppose the amplification prediction.

If metabolic measurements improve but later function does not, the recovery claim weakens once residual exposure and predefined limitations are addressed. If mast-cell outputs do not delay source-tissue recovery, a one-way effect could remain, but the feedback claim loses support. Luteolin activity without selective KHK effects would favor its independent pharmacology.

Biological replication across independent donors, effects defined in advance as meaningful, and enough precision to interpret a null result are essential. Replicate wells do not replace independent donors. Negative findings should delimit the tested mechanism, rather than prompt an undefined susceptible subgroup after the result is known.

8. What this could mean—and what remains unknown

The literature supports individual steps, not the complete proposed mechanism in MCAS. Kidney injury, food anaphylaxis, diabetic neuropathy, and intestinal inflammation provide experimental clues; they are different conditions.

Alternative explanations matter, especially in the intestine. Malabsorption, allergy, and microbial activity can produce diet-related symptoms independently of host KHK. Transferring irritable bowel syndrome-associated human microbiota into mice linked microbial histamine production to visceral hypersensitivity and mast-cell-related changes involving H4 receptors [37]. This does not establish a fructose-specific or KHK-dependent mechanism. Histamine levels alone cannot distinguish microbial production, impaired clearance, and mast-cell release. Serum urate, circulating mitochondrial DNA, and symptoms are also too nonspecific to identify a KHK-dependent subgroup by themselves.

Clinical relevance requires objectively characterized mast-cell activation and evidence that the proposed pathway operates in those patients. Selective KHK inhibitors have entered human metabolic studies, including first-in-human LY3522348 work, but these studies do not establish benefit in MCAS [38]. The present hypothesis provides no basis for a luteolin dose recommendation, a supplement treatment claim, or withdrawal of established care.

An initial human study could examine cells or clinically obtained tissue from confirmed idiopathic MCAS, secondary mast-cell activation, symptomatic people who do not meet MCAS criteria, and healthy controls. Researchers should specify the diagnostic framework, define any proposed responder subgroup before confirmatory analysis, and seek independent reproduction. They should record medications, diabetes, renal function, tissue site, and recent inflammatory events. Dietary history must include prior exposure and symptom-driven avoidance: low current intake may reflect adaptation to illness. Sampling across episodes could test whether pathway activity tracks responsiveness, but experimental intervention would still be needed to establish causality. The initial cellular test does not require provoking symptoms in patients.

The central question is whether continuing metabolic activity in one tissue keeps mast cells unusually responsive—and whether relieving that input helps both recover. A positive result would identify a candidate amplifier, not a universal cause of MCAS. A well-controlled negative result would narrow the KHK hypothesis and its contribution to the broader recovery framework. Either outcome would advance

the argument beyond shared inflammatory markers or improvement with a compound that has several targets.

Proposed step	What the evidence establishes	What would test the connection?
KHK-dependent fructose processing stresses source tissue	Selected epithelial models show this effect; its role in MCAS remains untested [13][14].	Verify metabolic flux and compare selective inhibition with genetic interruption.
Stressed tissue releases signals that reach mast cells	The KHK-dependent connection remains proposed.	Measure released signals and test their effects at the concentrations produced.
Those signals increase mast-cell responses	ATP and mitochondrial material act in experimental systems; dose and context matter [22][24][26].	Separate direct triggering, amplification of a challenge, and responses after exposure ends.
Mast-cell products delay source-tissue recovery	This return effect remains untested in the proposed system.	Change mast-cell output and measure later source-tissue function.
Mast cells process fructose directly through KHK	This direct route remains unestablished in the evidence reviewed here; enzyme version, protein, and flux require verification.	Verify activity within mast cells and interrupt their KHK separately.
Luteolin acts through more than one pathway	Mast-cell, KHK, and CD38 evidence are separate; simultaneous human target engagement is unknown [14][32][36].	Compare selective interventions and test luteolin after KHK loss.

Table 1. The proposed mechanism and how to test it

The evidence supports components of the proposal. It does not establish the complete sequence in one system.

Statements and Declarations

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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 formulation is evaluated, and this article does not establish the clinical efficacy or human KHK-inhibitory activity of any LIV3 Health product.

Ethics

This article reports a literature-based conceptual synthesis and proposed experiments. It reports no participant recruitment, animal experiments, or identifiable clinical data. Ethics approval and participant consent are not applicable to the work reported.

Data Availability

No new datasets were generated or analyzed for the work reported in this article. The evidence discussed is available in the cited literature.

Author Contributions

Christopher Ryan Mearns conceived and developed the hypothesis, directed the literature synthesis, and guided the interpretation and revision of the manuscript. 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 is responsible for the interpretation, accuracy, and final content. No generative-AI images are included.

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