



— YOUTUBE RESEARCH SUMMARY

Research Summary: Stress Chemistry and Gut Barrier Disruption

As featured in Dr. Kenny Mittelstadt's video: [Why Your Gut Health Protocol Keeps Failing \(It's Not Your Gut\)](#)

— Research Context

Persistent gut symptoms after a repair protocol are often signals from the whole body, not evidence that the gut itself needs more intervention. The research below maps the documented pathways between stress chemistry, nervous system activity, and intestinal barrier function, and points to why treating the gut in isolation can produce results that do not hold. These studies connect what the gut is showing to what the rest of the system has been managing. The goal is a clearer picture of how upstream inputs shape gut barrier function, and why the sequencing of that investigation changes outcomes for patients who have stalled.

— Key Findings from the Research

STUDY 1 • PMID 37756251

Leigh et al. published a comprehensive review in *The Journal of Physiology* examining how acute and chronic stress affects gut physiology across multiple levels. Chronic stress structurally impairs the gut barrier, increasing its permeability. It alters the enteric nervous system, the web of nerves embedded in the gut wall that runs digestion largely on its own, and shifts the microbial community through the gut-brain axis. The review traced the chain of physiological events connecting sustained stress to measurable changes in gut barrier function. The clinical implication is direct: a repair protocol is working against a system that has not shifted when the stress load producing these changes remains active.

STUDY 2 • PMID 36806451

Zhang et al. examined the connection between psychological stress, gut homeostasis, and the HPA axis, the brain-adrenal communication loop governing the body's stress response. Corticotropin-releasing factor (CRF), released when stress is sustained, directly disrupts the gut's epithelial barrier, the single-cell lining separating the gut interior from the rest of the body. CRF increases permeability in that lining and activates mast cells and neutrophils in the gut wall, keeping the local inflammatory environment chronically elevated. This is a documented pathway from sustained stress chemistry to tight junction opening. The mechanism explains why glutamine supplementation can hit a ceiling when the HPA axis is still running the chemistry of sustained threat.

STUDY 3 • PMID 37505311

Di Vincenzo et al. published a narrative review in *Internal and Emergency Medicine* mapping the upstream inputs driving intestinal barrier disruption, including oxidative stress, dysbiosis, dietary triggers, and toxic exposures, and connecting that disruption to systemic inflammatory and autoimmune conditions. As a narrative review, it synthesizes existing research rather than testing an intervention, so it identifies plausible connections without specifying which upstream driver to address first in a specific patient. That sequencing remains clinical judgment. The review adds to the overall picture by establishing that gut barrier disruption is rarely the product of a single input, and that its downstream effects extend well beyond digestion.



— Functional Medicine Connections

The gut wall's permeability responds continuously to signals from the nervous system, the immune system, and the broader metabolic environment. Think of it as a dimmer switch rather than an on-off switch. The level of permeability is being adjusted in real time based on what the whole system is managing.

When the cumulative load of inputs, including stress chemistry, immune activation, toxic exposure, and depleted energy reserves, exceeds what the system can adapt to, the tight junctions open. They are doing exactly what they are designed to do under those conditions. The permeability is the report, the gut's readable signal that the whole system has crossed a threshold.

Investigating upstream systems before or alongside gut-specific repair changes the outcome for patients who have stalled. The four categories worth mapping are: stress physiology and nervous system tone; immune burden including unresolved infections or post-viral dysregulation; toxic load, with mold exposure as one of the most commonly missed inputs; and energy capacity, since a body in metabolic triage does not prioritize tissue repair. The goal is to identify which input is carrying the highest load in that person's system, because that is the factor determining whether the gut gets to heal or keeps reflecting the same terrain. Zonulin, a protein the body releases when tight junctions are opening, appears as a lab marker in many of these cases. Its presence points toward the investigation rather than being the problem to solve in isolation.

— Practical Reflections & Takeaways

If you have done a gut protocol and felt genuine improvement that later faded, it may be worth asking: what was happening in your life in the months leading up to when symptoms returned? Sleep, stress load, a significant transition, an illness, or a new environmental exposure can all be meaningful data points.

The gut tends to be one of the most readable places in the body for what the whole system is carrying. If your gut keeps sending the same signal despite real effort at the gut level, it may be inviting you to look at what else the system has been managing that has not yet been part of the conversation.

— References

Leigh, S. J., Uhlig, F., Wilmes, L., et al. The impact of acute and chronic stress on gastrointestinal physiology and function: a microbiota-gut-brain axis perspective. *The Journal of Physiology*. 2023;601(20):4491-4538. PMID: 37756251.

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