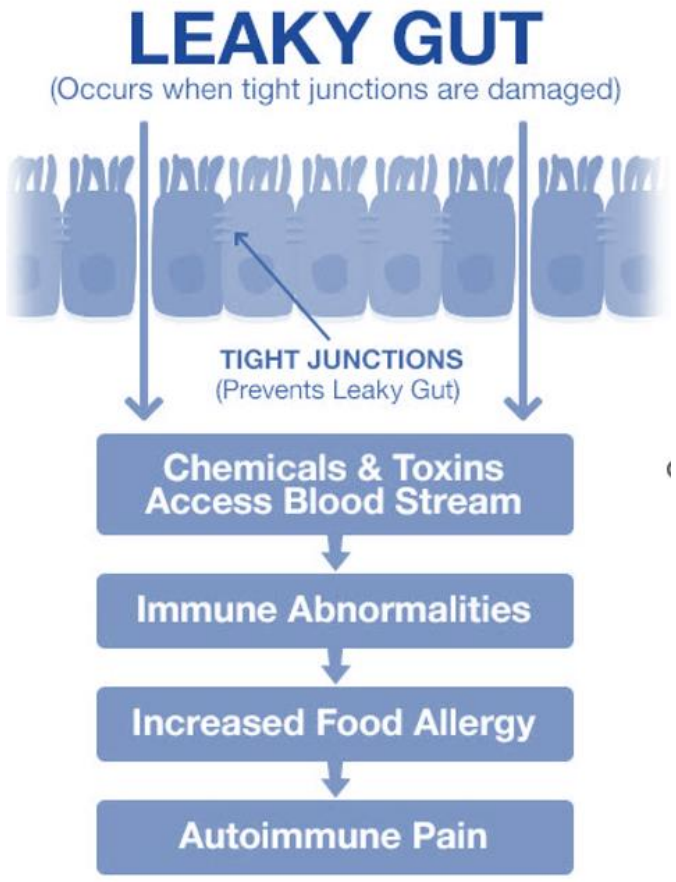

The Ultimate Guide

Leaky Gut

Does Leaky Gut Exist?

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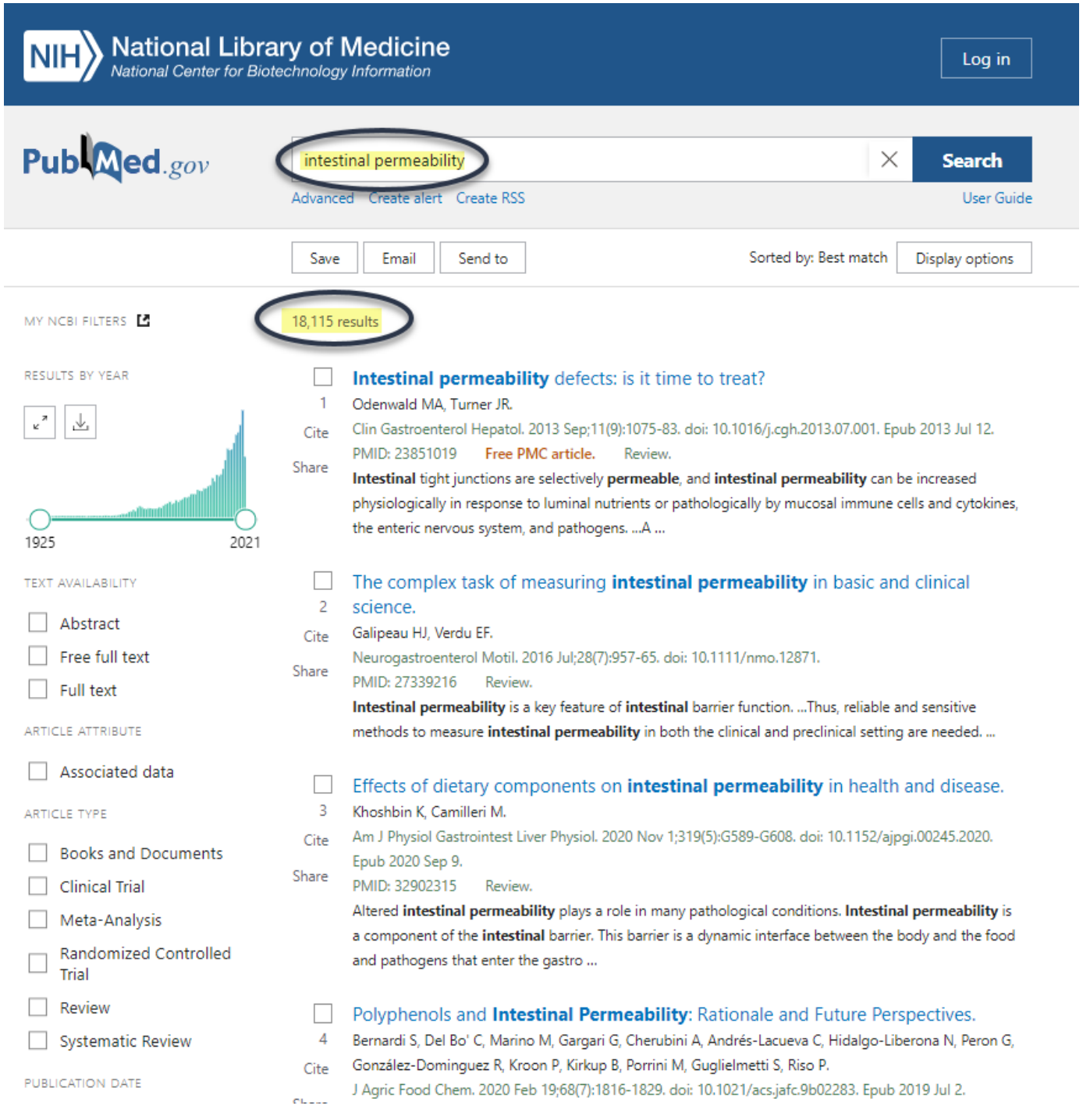

National Library of Medicine Research on Gluten and "Leaky Gut"- AKA Intestinal Permeability

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1. A low-**gluten** diet induces changes in the **intestinal** microbiome of healthy Danish adults
Lea B. S. Hansen, Henrik M. Roager, Nadja B. Søndertoft, Rikke J. Gøbel, Mette Kristensen, Mireia Vallès-Colomer, Sara Vieira-Silva, Sabine Ibrügger, Mads V. Lind, Rasmus B. Mærkedahl, Martin I. Bahl, Mia L. Madsen, Jesper Havelund, Gwen Falony, Inge Tetens, Trine Nielsen, Kristine H. Allin, Henrik L. Frandsen, Bolette Hartmann, Jens Juul Holst, Morten H. Sparholt, Jesper Holck, Andreas Blennow, Janne Marie Moll, Anne S. Meyer, Camilla Hoppe, Jørgen H. Poulsen, Vera Carvalho, Domenico Sagnelli, Marlene D. Dalgaard, Anders F. Christensen, Magnus Christian Lydolph, Alastair B. Ross, Silas Villas-Bôas, Susanne Brix, Thomas Sicheritz-Pontén, Karsten Buschard, Allan Linneberg, Jüri J. Rumessen, Claus T. Ekstrøm, Christian Ritz, Karsten Kristiansen, H. Bjørn Nielsen, Henrik Vestergaard, Nils J. Færgeman, Jeroen Raes, Hanne Frøkiær, Torben Hansen, Lotte Lauritzen, Ramneek Gupta, Tine Rask Licht, Oluf Pedersen
Nat Commun. 2018; 9: 4630. Published online 2018 Nov 13. doi: 10.1038/s41467-018-07019-x
PMCID: PMC6234216
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2. Dietary **Gluten** as a Conditioning Factor of the Gut Microbiota in Celiac Disease
Karla A Bascuñán, Magdalena Araya, Leda Roncoroni, Luisa Doneda, Luca Elli
Adv Nutr. 2020 Jan; 11(1): 160–174. Published online 2019 Aug 9. doi: 10.1093/advances/nmz080
PMCID: PMC7442381
Article PubReader PDF–377K Cite

3. A New Proposal for the Pathogenic Mechanism of Non-Coeliac/Non-Allergic **Gluten**/Wheat Sensitivity: Piecing Together the Puzzle of Recent Scientific Evidence
Valentina Leccioli, Mara Oliveri, Marcello Romeo, Massimiliano Berretta, Paola Rossi
Nutrients. 2017 Nov; 9(11): 1203. Published online 2017 Nov 2. doi: 10.3390/nu9111203
PMCID: PMC5707675

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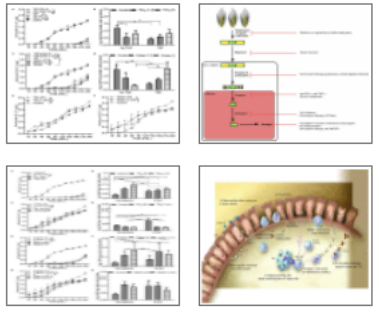

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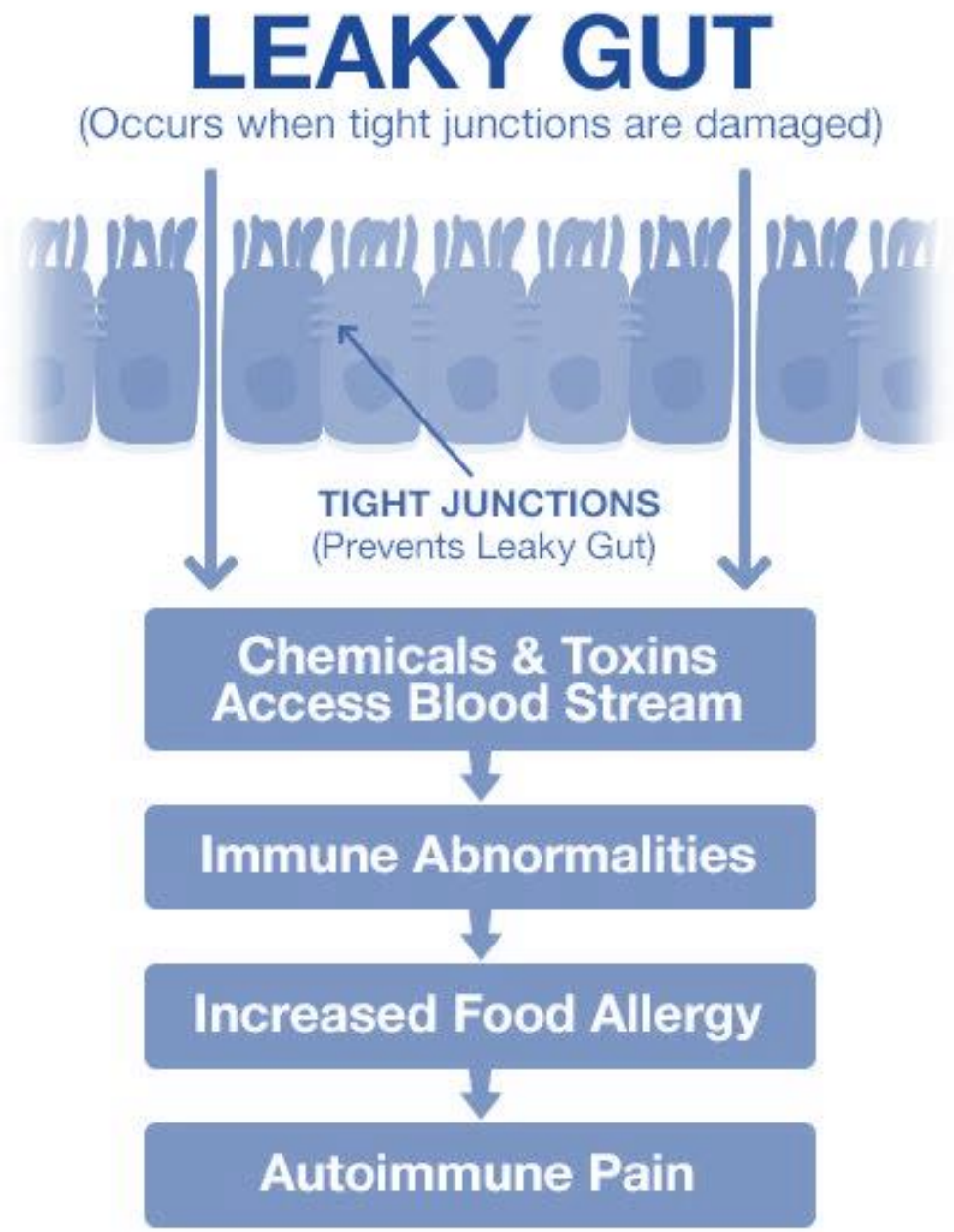
What Does Leaky Gut Damage Do?

- Overstimulates the immune system
- Allows bacterial and viral toxins access to the central circulation
- Causes allergic hypersensitivity to foods
- Sets the stage for Molecular Mimicry
- Linked to abnormal microbiome
- Inflammation of the GI Tract
- Malabsorption of vitamins, minerals, and other nutrients



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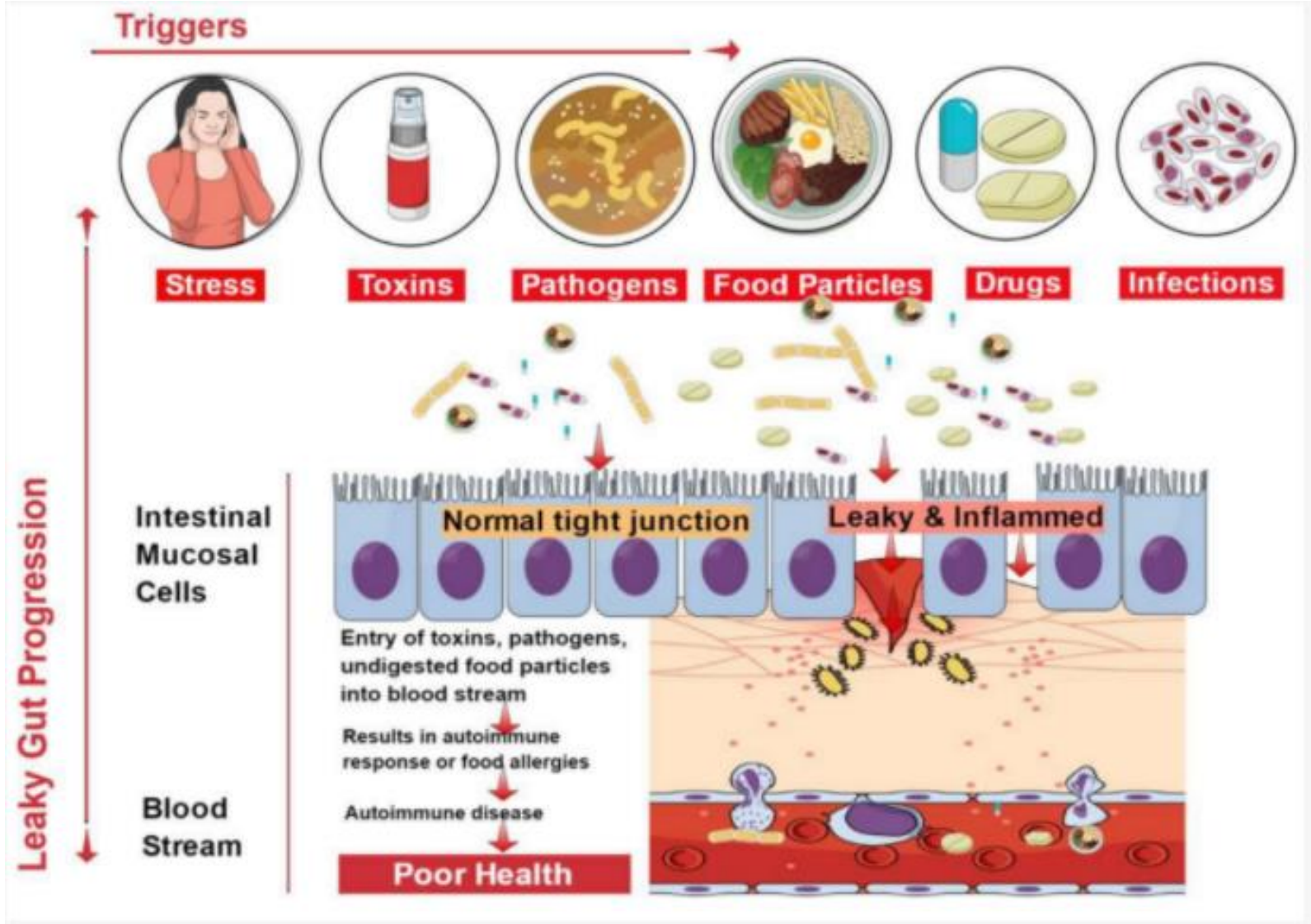
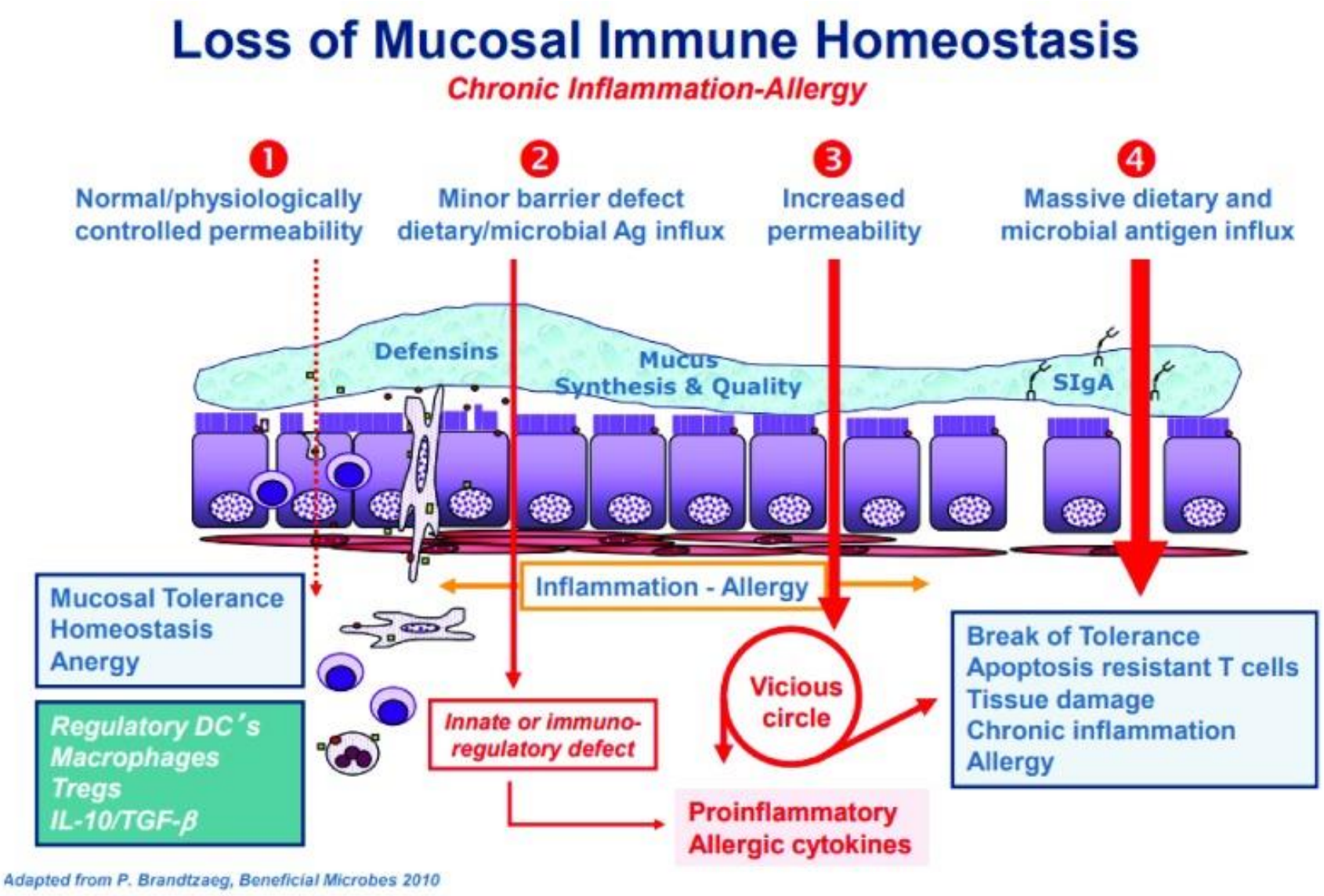


Image From: Paray BA, Albeshr MF, Jan AT, Rather IA. Leaky Gut and Autoimmunity: An Intricate Balance in Individuals Health and the Diseased State. International Journal of Molecular Sciences. 2020; 21(24):9770.

Leaky Gut…



Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Res*. 2020;9:F1000 Faculty Rev-69.

Or if we want to keep it simple…

Poop, food particles, and microbial toxins leak into your blood stream and poison your body slowly over time.

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Leaky Gut Consequences…

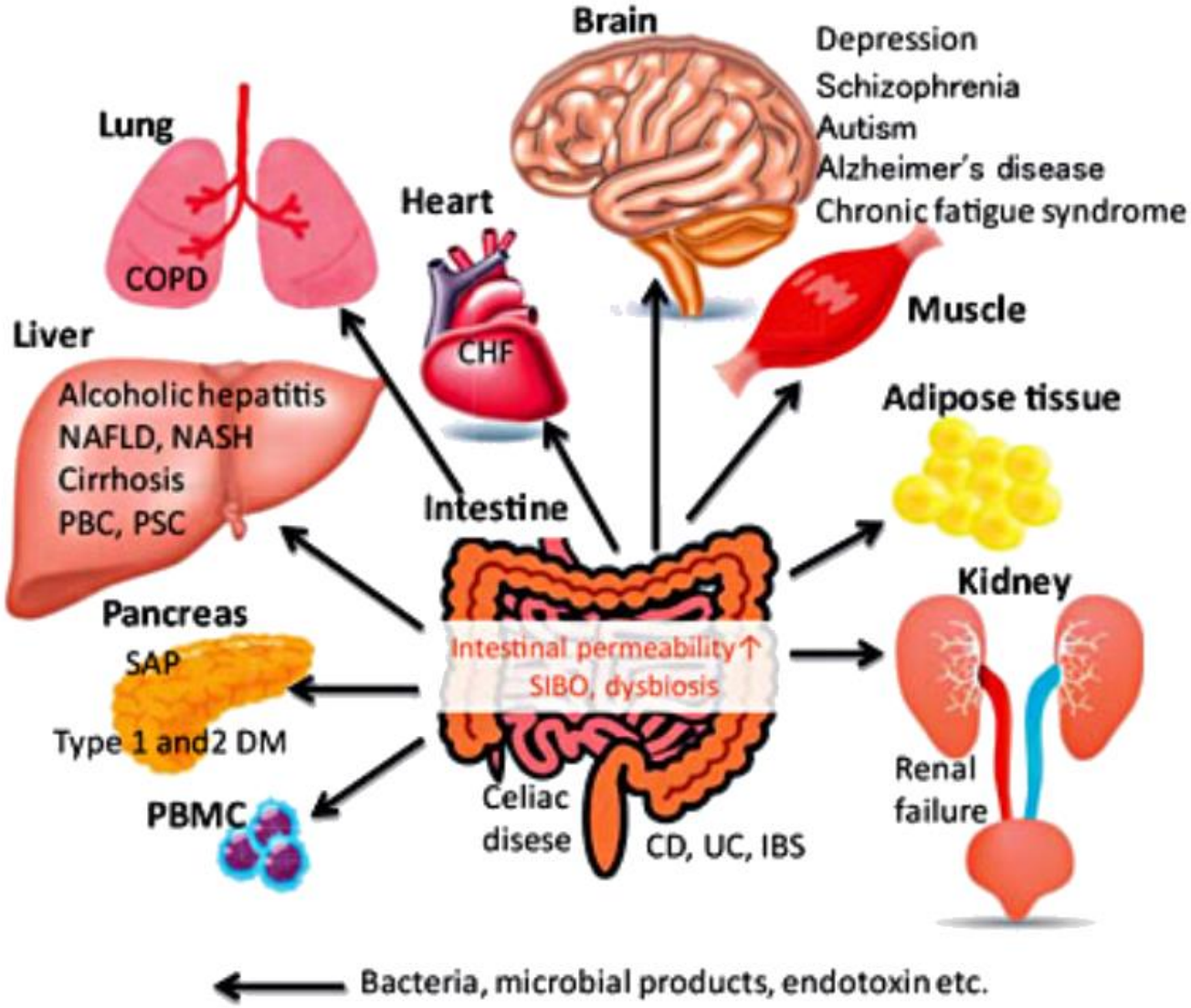

Image from: Fukui H. Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation? Inflamm Intest Dis. 2016 Oct;1(3):135-145.

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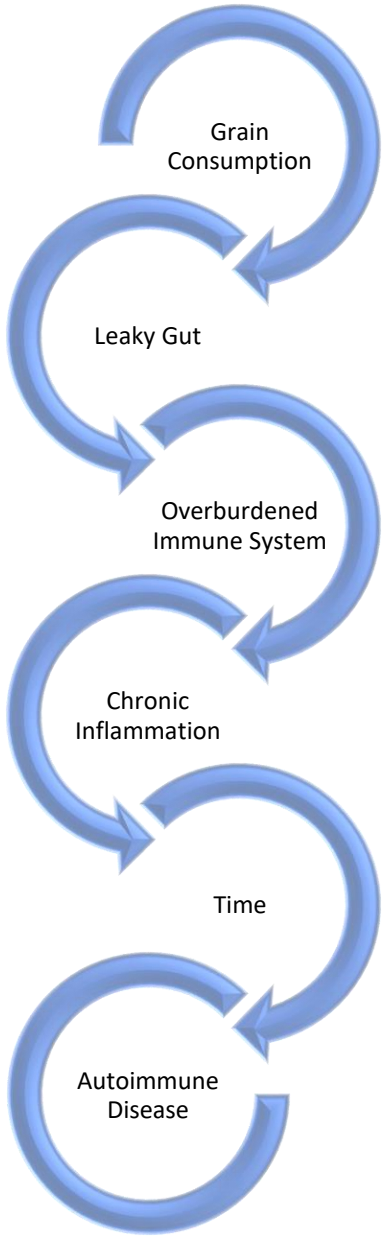
Leaky Gut → Autoimmunity

- Intestinal Hyperpermeability
- 70-80% of the immune system is in the gut



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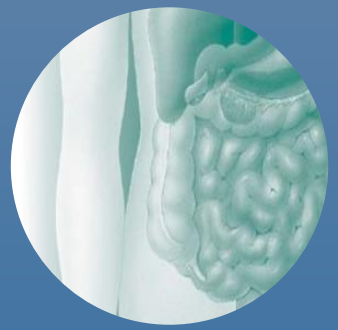
5 Primary Barriers of The GI Tract



GALT Immune

Tight Junctions

Mucosal IgA

Friendly Bacteria

Stomach Acid

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KNOWN CAUSES OF LEAKY GUT

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www.DrPeterOsborne.com

Gluten Free SOCIETY
www.GlutenFreeSociety.org

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3. K. de Punder and L. Pruimboom, "The Dietary Intake of Wheat and Other Cereal Grains and Their Role in Inflammation," Nutrients 5, no. 3 (2013): 771–87.
4. K. F. Csáki, "Synthetic Surfactant Food Additives Can Cause Intestinal Barrier Dysfunction," Medical Hypotheses 76, no. 5 (2011): 676–81.
5. M. Lamprecht and A. Frauwallner, "Exercise, Intestinal Barrier Dysfunction and Probiotic Supplementation," Medicine and Sport Science: Acute Topics in Sport Nutrition 59 (2012): 47–56.
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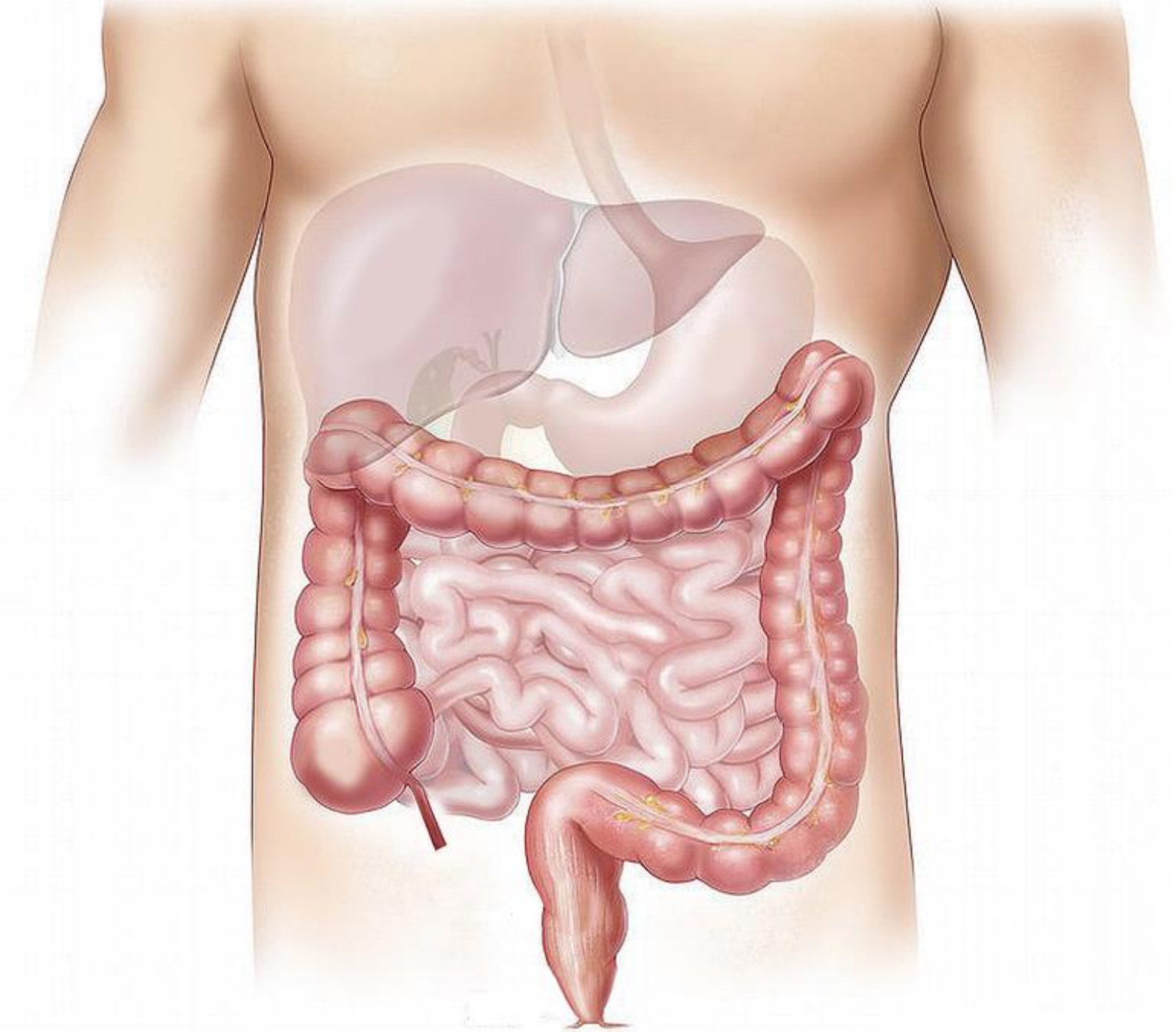


- Alcohol
- Fructose
- Sleep Disruption
- Nutritional Deficiencies
- Mold Toxins
- Food Additives
- Toxic Metals

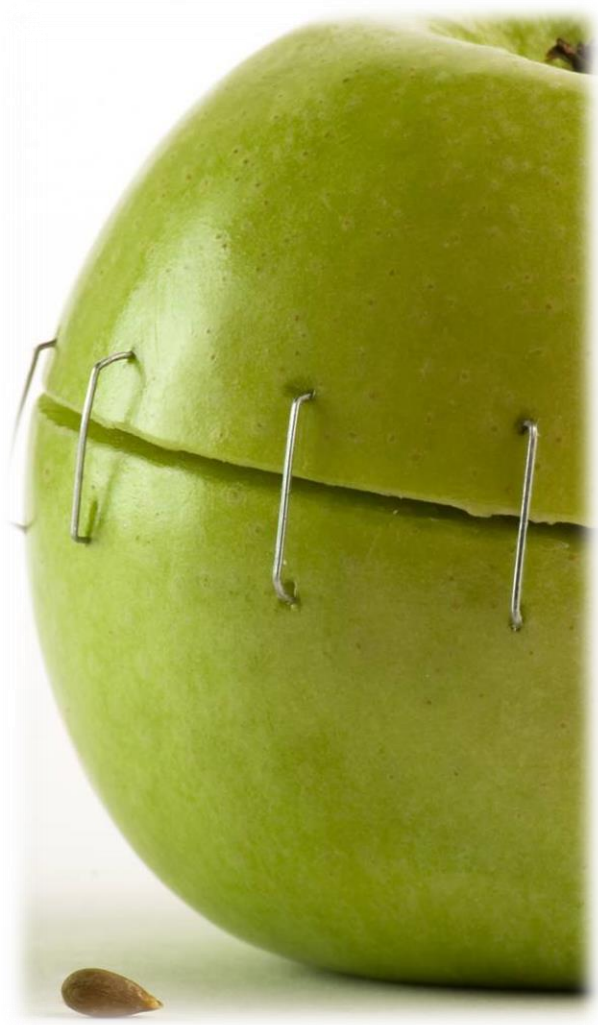
WHY DO WE EAT?

- Energy
- To promote normal tissue repair, growth, and balance.
- Maintain nourishment and function of the body

If you poison your gut long enough, it will break.

Frood…

- Aside from the possibility of reacting to real food…
- The FDA has approved approximately **3,000** food additives, preservatives, and colorings.
- The average person ingests **150 lbs.** of additives every year.
- Many commonly eaten foods are genetically modified or contain genetically modified ingredients.



TOXINS IN FOOD - Herbicides, Pesticides, Steroids, Hormones, Antibiotics, and Excitotoxins

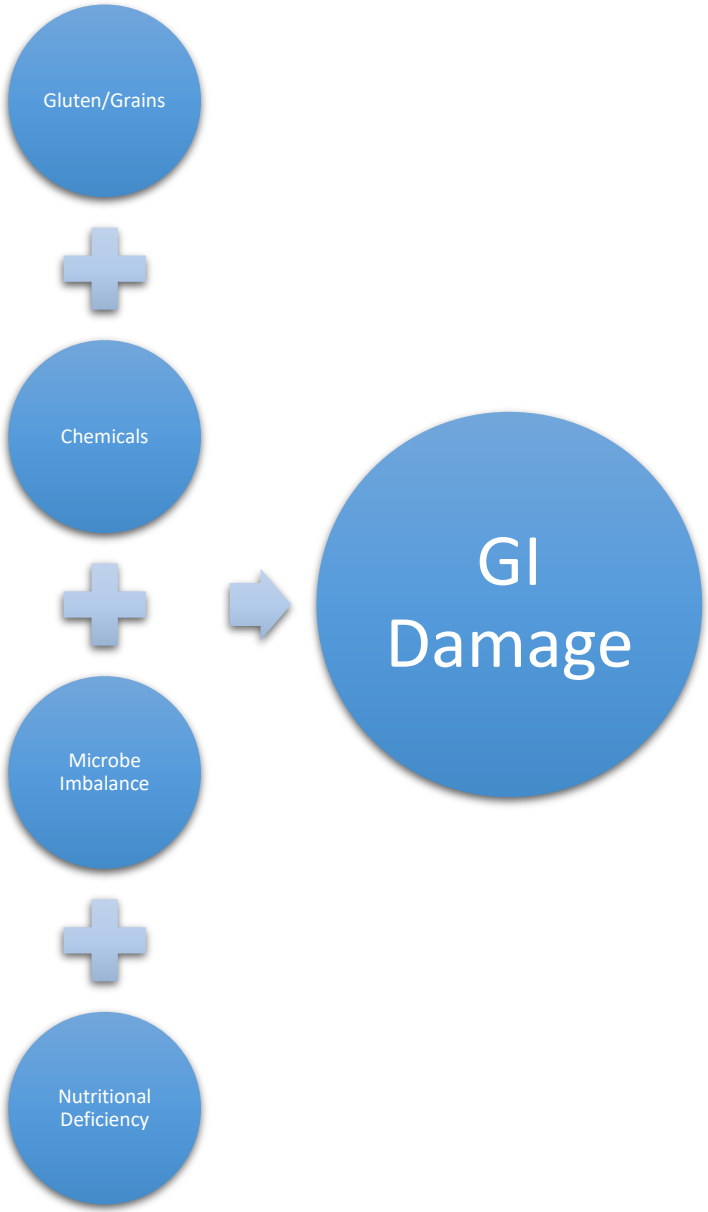
- It takes approximately 5 to 8 pounds of chemically sprayed grain to produce 1 pound of beef. Therefore, you will ingest considerably more cancer-causing chemicals from meat than from fruit and vegetables.
- On average, one glass of inorganic, store-bought milk contains the residue of about a hundred different antibiotics. Once in our bodies, these antibiotics ultimately weaken our immune system.

Compounding Damage…

- 4 billion prescription drugs are ingested in the U.S. each year.
- 70,000 chemicals are used commercially.
- 3,000+ chemicals are added to our food supply.
- 10,000+ chemicals are used in food processing, preserving, and storage.
- The EPA Estimates that our homes are now 5 to 100 times more toxic than outdoor air.

4 Horseman of the GI Apocalypse…

Let's Get Bobby to Dress up this image



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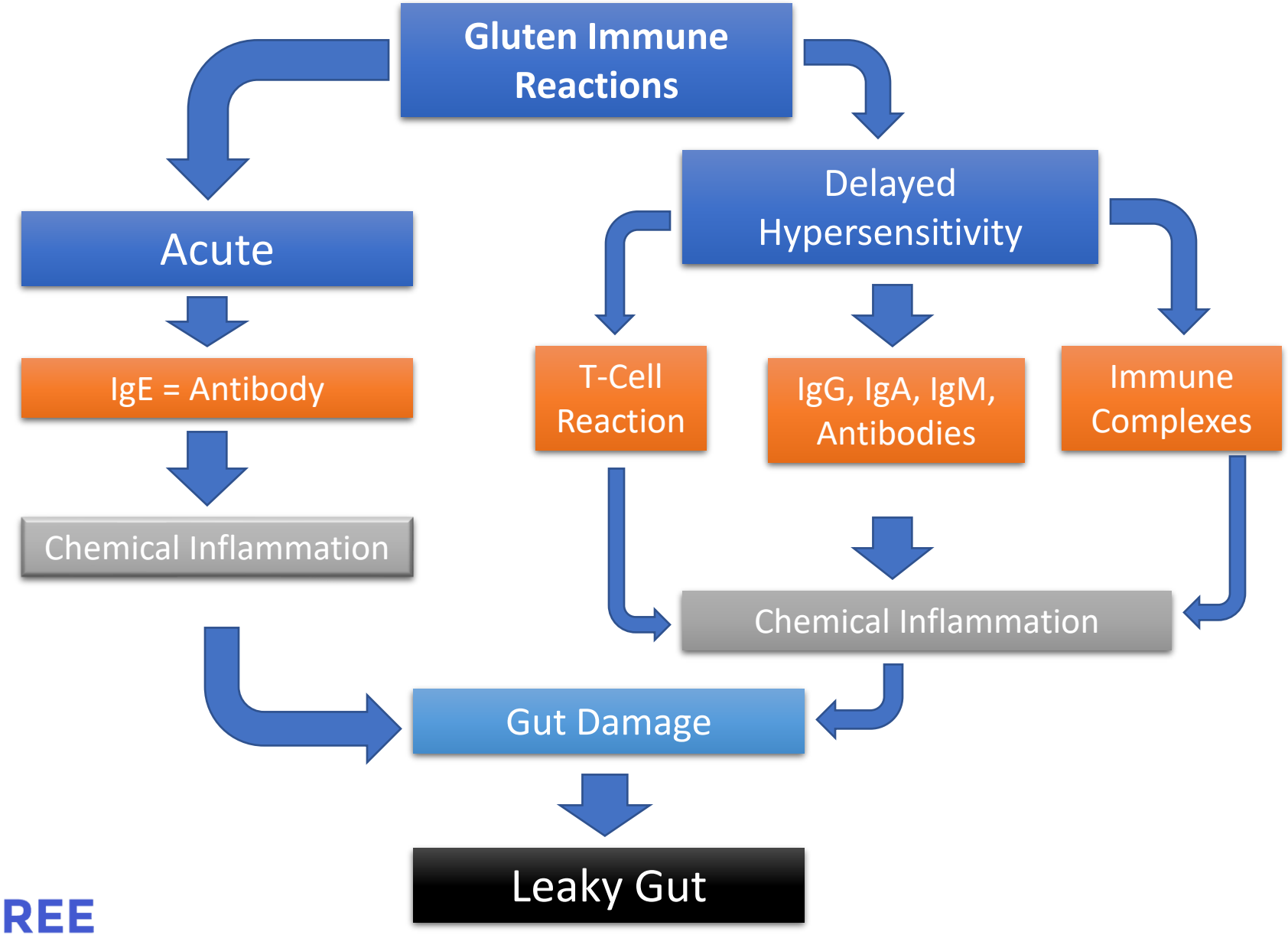

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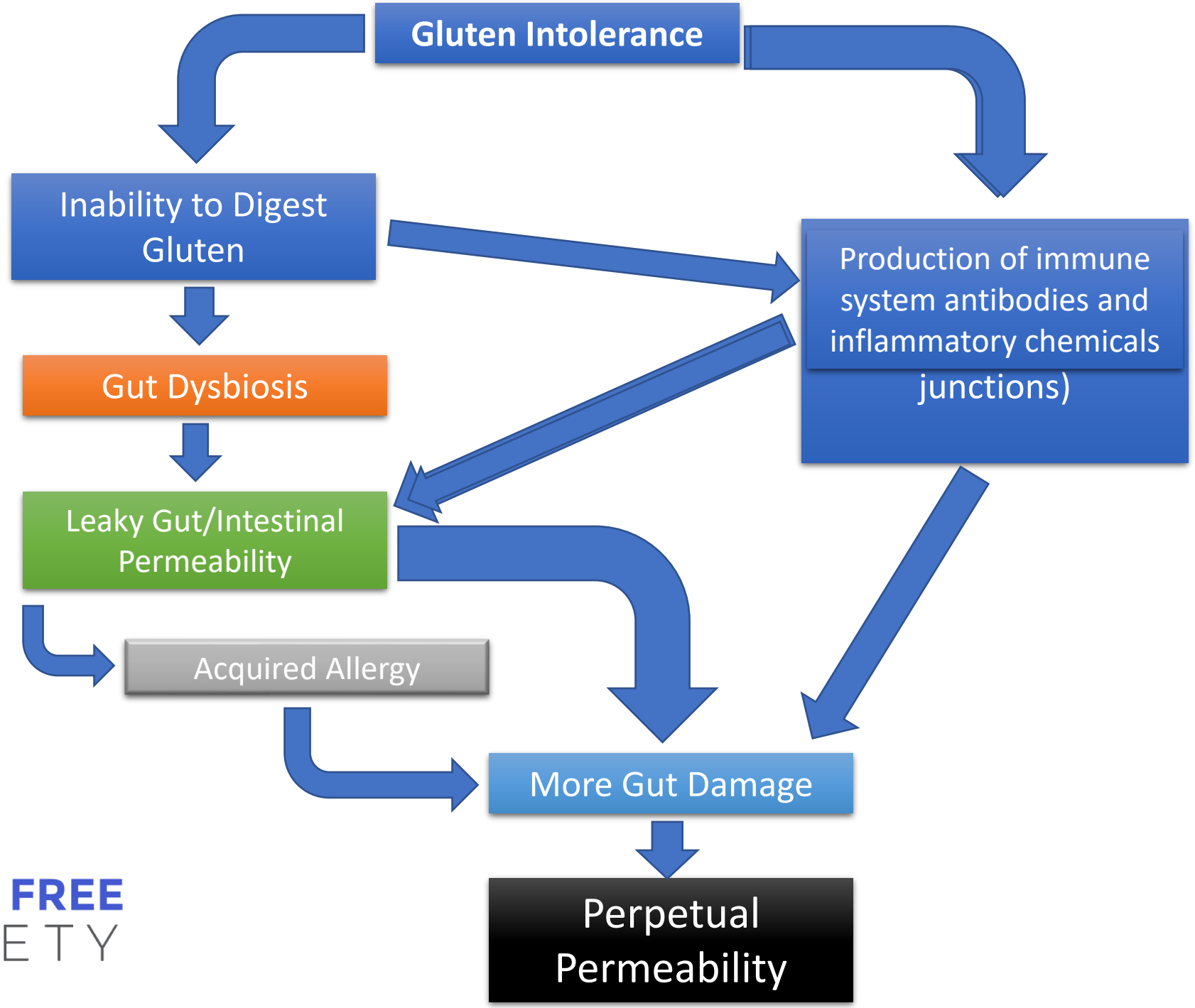

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› Scand J Gastroenterol. 2006 Apr;41(4):408-19. doi: 10.1080/00365520500235334.

Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines

Sandro Drago [1], Ramzi El Asmar, Mariarosaria Di Pierro, Maria Grazia Clemente, Amit Tripathi, Anna Sapone, Manjusha Thakar, Giuseppe Iacono, Antonio Carroccio, Cinzia D'Agate, Tarcisio Not, Lucia Zampini, Carlo Catassi, Alessio Fasano

Affiliations + expand

PMID: 16635908 DOI: 10.1080/00365520500235334

Abstract

Objective: Little is known about the interaction of gliadin with intestinal epithelial cells and the mechanism(s) through which gliadin crosses the intestinal epithelial barrier. We investigated whether gliadin has any immediate effect on zonulin release and signaling.

Material and methods: Both ex vivo human small intestines and intestinal cell monolayers were exposed to gliadin, and zonulin release and changes in paracellular permeability were monitored in the presence and absence of zonulin antagonism. Zonulin binding, cytoskeletal rearrangement, and zonula occludens-1 (ZO-1) redistribution were evaluated by immunofluorescence microscopy. Tight junction occludin and ZO-1 gene expression was evaluated by real-time polymerase chain reaction (PCR).

Results: When exposed to gliadin, zonulin receptor-positive IEC6 and Caco2 cells released zonulin in the cell medium with subsequent zonulin binding to the cell surface, rearrangement of the cell cytoskeleton, loss of occludin-ZO1 protein-protein interaction, and increased monolayer permeability. Pretreatment with the zonulin antagonist FZI/0 blocked these changes without affecting zonulin release. When exposed to luminal gliadin, intestinal biopsies from celiac patients in remission expressed a sustained luminal zonulin release and increase in intestinal permeability that was blocked by FZI/0 pretreatment. Conversely, biopsies from non-celiac patients demonstrated a limited, transient zonulin release which was paralleled by an increase in intestinal permeability that never reached the level of permeability seen in celiac disease (CD) tissues. Chronic gliadin exposure caused down-regulation of both ZO-1 and occludin gene expression.

Conclusions: Based on our results, we concluded that gliadin activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules.

Gastroenterology. 2008 July ; 135(1): 194–204.e3. doi:10.1053/j.gastro.2008.03.023.

Gliadin Induces an Increase in Intestinal Permeability and Zonulin Release by Binding to the Chemokine Receptor CXCR3

Karen M. Lammers[*,‡], **Ruliang Lu**[*,‡], **Julie Brownley**[*,‡], **Bao Lu**[§], **Craig Gerard**[§], **Karen Thomas**[‖], **Prasad Rallabhandi**[‖], **Terez Shea-Donohue**[*], **Amir Tamiz**[¶], **Sefik Alkan**[¶], **Sarah Netzel-Arnett**[#], **Toni Antalis**[#], **Stefanie N. Vogel**[‖], and **Alessio Fasano**[*,‡]

[*]*Mucosal Biology Research Center, University of Maryland School of Medicine, Baltimore, Maryland* [‡]*Center for Celiac Research, University of Maryland School of Medicine, Baltimore, Maryland* [§]*Children's Hospital Boston, Boston, Massachusetts* [‖]*Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, Maryland* [¶]*Alba Therapeutics Corporation, Baltimore, Maryland* [#]*Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, Maryland*

Abstract

Background & Aims—Celiac disease is an immune-mediated enteropathy triggered by gliadin, a component of the grain protein gluten. Gliadin induces an MyD88-dependent zonulin release that leads to increased intestinal permeability, a postulated early element in the pathogenesis of celiac disease. We aimed to establish the molecular basis of gliadin interaction with intestinal mucosa leading to intestinal barrier impairment.

Methods—α-Gliadin affinity column was loaded with intestinal mucosal membrane lysates to identify the putative gliadin-binding moiety. In vitro experiments with chemokine receptor CXCR3 transfectants were performed to confirm binding of gliadin and/or 26 overlapping 20mer α-gliadin synthetic peptides to the receptor. CXCR3 protein and gene expression were studied in intestinal epithelial cell lines and human biopsy specimens. Gliadin-CXCR3 interaction was further analyzed by immunofluorescence microscopy, laser capture microscopy, real-time reverse-transcription polymerase chain reaction, and immunoprecipitation/Western blot analysis. Ex vivo experiments were performed using C57BL/6 wild-type and CXCR3$^{-/-}$ mouse small intestines to measure intestinal permeability and zonulin release.

Results—Affinity column and colocalization experiments showed that gliadin binds to CXCR3 and that at least 2 α-gliadin 20mer synthetic peptides are involved in this binding. CXCR3 is expressed in mouse and human intestinal epithelia and lamina propria. Mucosal CXCR3 expression was elevated in active celiac disease but returned to baseline levels following implementation of a gluten-free diet. Gliadin induced physical association between CXCR3 and MyD88 in enterocytes. Gliadin increased zonulin release and intestinal permeability in wild-type but not CXCR3$^{-/-}$ mouse small intestine.

Conclusions—Gliadin binds to CXCR3 and leads to MyD88-dependent zonulin release and increased intestinal permeability.

› FEBS Lett. 2005 Aug 29;579(21):4851-5. doi: 10.1016/j.febslet.2005.07.066.

Rapid disruption of intestinal barrier function by gliadin involves altered expression of apical junctional proteins

Guy R Sander [1], Adrian G Cummins, Tanya Henshall, Barry C Powell

Affiliations + expand

PMID: 16099460 DOI: 10.1016/j.febslet.2005.07.066

Free article

Abstract

Coeliac disease is a chronic enteropathy caused by the ingestion of wheat gliadin and other cereal prolamines derived from rye and barley. In the present work, we investigated the mechanisms underlying altered barrier function properties exerted by gliadin-derived peptides in human Caco-2 intestinal epithelial cells. We demonstrate that gliadin alters barrier function almost immediately by decreasing transepithelial resistance and increasing permeability to small molecules (4 kDa). Gliadin caused a reorganisation of actin filaments and altered expression of the tight junction proteins occludin, claudin-3 and claudin-4, the TJ-associated protein ZO-1 and the adherens junction protein E-cadherin.

Nutrients. 2015 Mar; 7(3): 1565–1576. PMCID: PMC4377866
Published online 2015 Feb 27. doi: 10.3390/nu7031565 PMID: 25734566

Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity

Justin Hollon,[1,*] Elaine Leonard Puppa,[2] Bruce Greenwald,[3] Eric Goldberg,[3] Anthony Guerrerio,[4] and Alessio Fasano[5]

This study demonstrates that gliadin exposure induces an increase in intestinal permeability in all individuals, regardless of whether or not they have celiac disease. The results of this study suggest that gluten exposure leads to altered barrier function in both ACD and GS, resulting in an exaggerated increase in intestinal permeability when compared to RCD. The intestinal mucosal secretion of IL-10 from the basolateral surface seen in NC subjects in this study was not observed in those with RCD or GS. Specific laboratory markers for GS are still necessary to allow for a more objective definition of GS and further research into GS disorders would benefit from double-blind, placebo-controlled studies.

A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function

Maria I Vazquez-Roque [1], Michael Camilleri, Thomas Smyrk, Joseph A Murray, Eric Marietta, Jessica O'Neill, Paula Carlson, Jesse Lamsam, Denise Janzow, Deborah Eckert, Duane Burton, Alan R Zinsmeister

Affiliations + expand

PMID: 23357715 PMCID: PMC3633663 DOI: 10.1053/j.gastro.2013.01.049

Free PMC article

Abstract

Background & aims: Patients with diarrhea-predominant irritable bowel syndrome (IBS-D) could benefit from a gluten-free diet (GFD).

Methods: We performed a randomized controlled 4-week trial of a gluten-containing diet (GCD) or GFD in 45 patients with IBS-D; genotype analysis was performed for HLA-DQ2 and HLA-DQ8. Twenty-two patients were placed on the GCD (11 HLA-DQ2/8 negative and 11 HLA-DQ2/8 positive) and 23 patients were placed on the GFD (12 HLA-DQ2/8 negative and 11 HLA-DQ2/8 positive). We measured bowel function daily, small-bowel (SB) and colonic transit, mucosal permeability (by lactulose and mannitol excretion), and cytokine production by peripheral blood mononuclear cells after exposure to gluten and rice. We collected rectosigmoid biopsy specimens from 28 patients, analyzed levels of messenger RNAs encoding tight junction proteins, and performed H&E staining and immunohistochemical analyses. Analysis of covariance models was used to compare data from the GCD and GFD groups.

Results: Subjects on the GCD had more bowel movements per day (P = .04); the GCD had a greater effect on bowel movements per day of HLA-DQ2/8-positive than HLA-DQ2/8-negative patients (P = .019). The GCD was associated with higher SB permeability (based on 0-2 h levels of mannitol and the lactulose:mannitol ratio); SB permeability was greater in HLA-DQ2/8-positive than HLA-DQ2/8-negative patients (P = .018). No significant differences in colonic permeability were observed. Patients on the GCD had a small decrease in expression of zonula occludens 1 in SB mucosa and significant decreases in expression of zonula occludens 1, claudin-1, and occludin in rectosigmoid mucosa; the effects of the GCD on expression were significantly greater in HLA-DQ2/8-positive patients. The GCD vs the GFD had no significant effects on transit or histology. Peripheral blood mononuclear cells produced higher levels of interleukin-10, granulocyte colony-stimulating factor, and transforming growth factor-α in response to gluten than rice (unrelated to HLA genotype).

Conclusions: Gluten alters bowel barrier functions in patients with IBS-D, particularly in HLA-DQ2/8-positive patients. These findings reveal a reversible mechanism for the disorder. Clinical trials.govNCT01094041.

This is Your Gut After Years of Gluten….

This is YOU when you are first going gluten free

Gluten & Grain – The Path to Disease

Undiagnosed – typically little symptoms…

- Gluten induced damage combined with other poor choices…

Progression to subclinical problems

- Intestinal permeability (Leaky gut)
- Acquired food and environmental allergies

Recognition of problem but not it's origin

- Illness and disease
- Autoimmunity and inflammatory changes

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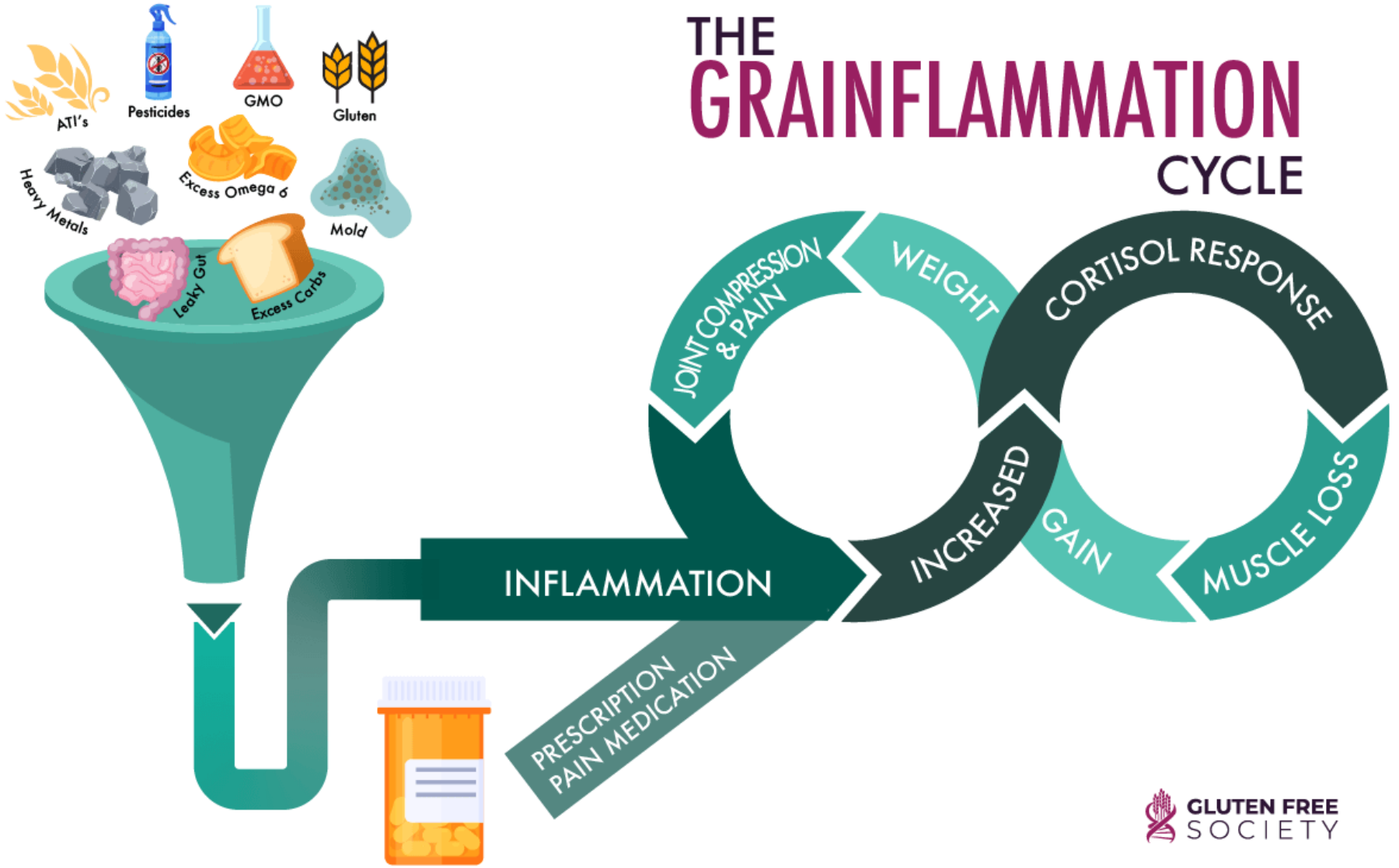
THE GRAINFLAMMATION CYCLE



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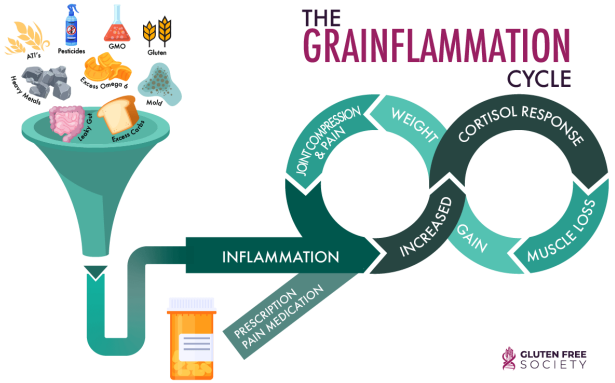

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Chem Res Toxicol. 2017 April 17; 30(4): 996–1005. doi:10.1021/acs.chemrestox.6b00401.

Multi-Omics Reveals that Lead Exposure Disturbs Gut Microbiome Development, Key Metabolites and Metabolic Pathways

Bei Gao[†], **Liang Chi**[‡], **Ridwan Mahbub**[†], **Xiaoming Bian**[†], **Pengcheng Tu**[‡], **Hongyu Ru**[§], and **Kun Lu**[‡,*]

[†]Department of Environmental Health Science, University of Georgia, Athens, GA, 30602

[‡]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599

[§]Department of Population Health and Pathobiology, North Carolina State University, Raleigh, NC, 27607

Abstract

Lead exposure remains a global public health issue, and the recent Flint water crisis has renewed public concern about lead toxicity. The toxicity of lead has been well established in a variety of systems and organs. The gut microbiome has been shown to be highly involved in many critical physiological processes, including food digestion, immune system development and metabolic homeostasis. However, despite the key role of the gut microbiome in human health, the functional impact of lead exposure on the gut microbiome has not been studied. The aim of this study is to define gut microbiome toxicity induced by lead exposure in C57BL/6 mice using multi-omics approaches, including 16S rRNA sequencing, whole genome metagenomics sequencing and gas chromatography-mass spectrometry (GC-MS) metabolomics. 16S rRNA sequencing revealed that lead exposure altered the gut microbiome trajectory and phylogenetic diversity. Metagenomics sequencing and metabolomics profiling showed that numerous metabolic pathways, including vitamin E, bile acids, nitrogen metabolism, energy metabolism, oxidative stress and the defense/detoxification mechanism, were significantly disturbed by lead exposure. These perturbed molecules and pathways may have important implications for lead toxicity in the host. Taken together, these results demonstrated that lead exposure not only altered gut microbiome community structures/diversity but also greatly affected metabolic functions, leading to gut microbiome toxicity.

Mercury induces tight junction alterations and para-cellular transport in colon epithelial cells through oxidative stress and thiol-redox dysregulation—protection by novel lipid-soluble thiol antioxidant, NBMI

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Aarti_Vala_Honors_Thesis_May2012_final.pdf (1.992Mb)

Creators:
Vala, Aarti

Advisor:
Parinandi, Narasimham

Keywords:
mercury
intestinal leak
leaky gut
heavy metal chelator
antioxidant

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2012-06

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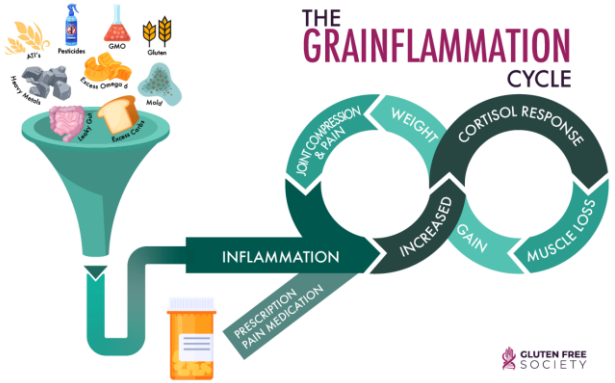
The Ohio State University. Department of Microbiology Honors Theses; 2012

Abstract:
Intestinal permeability, characterized as leaky-gut syndrome, is a debilitating gastrointestinal disorder that leads to inflammation and altered immune response. Tight junctions are crucial for cell-to-cell adhesion and regulation of paracellular transport of molecules across the intestinal epithelium. However, the exact mechanism of the leaky-gut state encountered in autistic spectrum disorders is not known. Mercury, both as inorganic and organic forms, has been identified as a serious environmental pollutant, occupational hazard, and pharmaceutical toxicant. Mercury, in the form of thimerosal in vaccines, has been implicated as one of the causative species of autism. Therefore, here, we hypothesized that mercury would cause intestinal epithelial cell tight junction alterations and paracellular hyperpermeability (leak) through oxidative stress and thiol-redox dysregulation which could lead to the leaky-gut condition. Hence, we investigated the mechanism of tight junction alteration and paracellular leak of macromolecules in the well-established in vitro intestinal (colon) epithelial Caco-2 cell model. We also identified efficacy of the thiol-redox stabilization drugs to protect against the mercury-induced damage in the Caco-2 cells in vitro. Our studies revealed that the two forms of mercury, methylmercury and thimerosal caused (i) dose- and time-dependent cytotoxicity (lactate dehydrogenase release, decreased mitochondrial integrity, and cell morphological alterations), (ii) loss of intracellular glutathione (GSH), (iii) increase in the formation of reactive oxygen species, (iv) loss of barrier dysfunction; (v) loss of cell proliferation, (vi) actin cytoskeletal rearrangement (actin stress fiber formation), (vii) tight-junction (ZO-1 protein and occludins) alterations, and (viii) increase in paracellular leak of macromolecules in Caco-2 cells in vitro. Mercury-induced cytotoxicity, tight junction alterations, and increase in paracellular leak were significantly attenuated by the novel lipophilic thiol-redox-stabilizing antioxidant and heavy metal chelator, N,N'-bis-(2-mercaptoethyl)isophthalamide (NBMI). For the first time, the results of the current study demonstrated that mercury (methylmercury and thimerosal) caused intestinal epithelial cell damage and macromolecule leak through thiol-redox dysregulation and oxidative stress which was effectively protected by the novel lipophilic thiol-redox stabilizer and heavy metal chelator, NBMI. Our findings emphasize the significance of altered cellular functioning by the intestinal epithelium upon exposure to mercuric agents, and pharmacological attenuation by the novel drug, NBMI.



Review > Environ Pollut. 2018 Apr;235:429-434. doi: 10.1016/j.envpol.2017.12.114. Epub 2018 Jan 5.

Gut as a target for cadmium toxicity

Alexey A Tinkov [1], Viktor A Gritsenko [2], Margarita G Skalnaya [3], Sergey V Cherkasov [2], Jan Aaseth [4], Anatoly V Skalny [5]

Affiliations + expand

PMID: 29310086 DOI: 10.1016/j.envpol.2017.12.114

Abstract

The primary objective of the present study was to review the impact of Cd exposure on gut microbiota and intestinal physiology, as well as to estimate whether gut may be considered as the target for Cd toxicity. The review is based on literature search in available databases. The existing data demonstrate that the impact of Cd on gut physiology is two-sided. First, Cd exposure induces a significant alteration of bacterial populations and their relative abundance in gut (increased Bacteroidetes-to-Firmicutes ratio), accompanied by increased lipopolysaccharide (LPS) production, reflecting changed metabolic activity of the intestinal microbiome. Second, in intestinal wall Cd exposure induces inflammatory response and cell damage including disruption of tight junctions, ultimately leading to increased gut permeability. Together with increased LPS production, impaired barrier function causes endotoxinemia and systemic inflammation. Hypothetically, Cd-induced increase gut permeability may also result in increased bacterial translocation. On the one hand, bacteriolysis may be associated with aggravation of endotoxemia. At the same time, together with Cd-induced impairment of macrophage inflammatory response, increased bacterial translocation may result in increased susceptibility to infections. Such a supposition is generally in agreement with the finding of higher susceptibility of Cd-exposed mice to infections. The changed microbiome metabolic activity and LPS-induced systemic inflammation may have a significant impact on target organs. The efficiency of probiotics in at least partial prevention of the local (intestinal) and systemic toxic effects of cadmium confirms the role of altered gut physiology in Cd toxicity. Therefore, probiotic treatment may be considered as the one of the strategies for prevention of Cd toxicity in parallel with chelation, antioxidant, and anti-inflammatory therapy.

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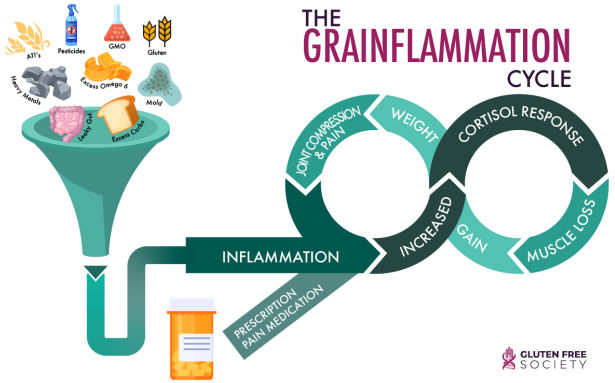

REVIEW

Exposure to inorganic arsenic can lead to gut microbe perturbations and hepatocellular carcinoma

Jonathan Choiniere[a], **Li Wang**[a,b,c,d,*]

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[b]*School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, China*
[c]*Veterans Affairs Connecticut Healthcare System, West Haven, CT 06516, USA*
[d]*Department of Internal Medicine, Section of Digestive Diseases, Yale University, New Haven, CT 06520, USA*

Abstract Arsenic is a carcinogenic environmental factor found in food and drinking water around the world. The mechanisms in which arsenic alters homeostasis are not fully understood. Over the past few decades, light has been shed on varying mechanisms in which arsenic induces cancer. Such mechanisms include gut microbe perturbations, genotoxic effects, and epigenetic modification. Gut microbe perturbations have been shown to increase the level of pathogen-associated molecular patterns such as lipopolysaccharide (LPS) leading to uncontained inflammation. Increase in inflammation is the major factor in cirrhosis leading to hepatocellular carcinoma. Alterations in gut permeability and metabolites have also been observed as a fallout of arsenic induced gut microbe modification. The guts proximity and interaction through portal flow make the liver susceptible to gut perturbations and ensuing inflammatory responses. Genotoxic and epigenetic dysregulation induced by arsenic and its toxic metabolites present a more direct mechanism that works synergistically with gut microbe perturbations to induce the incidence of cancers. These pathways combined could be some of the main causes of arsenic-induced carcinogenesis.

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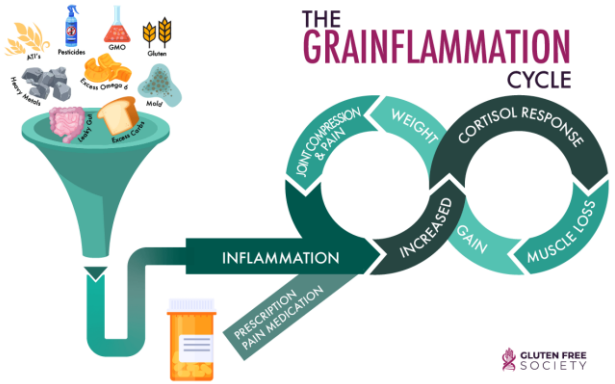

GLUTEN FREE SOCIETY

ILAR Journal, 2015, Vol. 56, No. 2, 218–227

doi: 10.1093/ilar/ilv018
Article

Xenobiotics: Interaction with the Intestinal Microflora

Kun Lu, Ridwan Mahbub, and James G. Fox

Kun Lu, PhD, is an Assistant Professor in the Department of Environmental Health Science at the University of Georgia, Athens, Georgia. Ridwan Mahbub, BSA, MS, was a graduate student in the laboratory of Dr. Kun Lu at University of Georgia, Athens, Georgia. James G. Fox, DVM, is currently Professor and Director of the Division of Comparative Medicine at the Massachusetts Institute of Technology, Cambridge, Massachusetts.

Address correspondence and reprint requests to Dr. Kun Lu, 140 Environmental Health Science Building, University of Georgia, Athens, GA 30602 or email kunlu@uga.edu.

Effects of Xenobiotics on the Gut Microbiome

Xenobiotics Alter the Gut Microbiome Community Structure

In general, xenobiotics have been known to alter the GM for some time (see, for example, George et al. 1989). However, recent developments in culture-free methods, such as 16S rRNA sequencing, have allowed us to actually profile the specific changes that occur in the GM community structure as a result of exposure to xenobiotics (Robinson and Young 2010). In this section, we will focus on studies that show the effects that several typical substances, such as antibiotics, pesticides, air pollutants, polychlorinated biphenyls (PCBs), and heavy metals, have on the GM structure. This is by no means a complete list of xenobiotics that could perturb the gut microbiome structures in different models.

Does Alcohol Increase Reactivity to Gluten?

primary source of the immunological response. A possible explanation may be that antigliadin antibodies arise in patients with genetic susceptibility (HLADQ2/DQ8 genotype) following a chronic immunological insult (alcohol) centered on the cerebellum. Alcohol has previously been associated with antibodies to transglutaminase and is known to evoke an immunogenic reaction[3].

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PLoS One. 2013; 8(10): e77638. PMCID: PMC3817350
Published online 2013 Oct 15. doi: 10.1371/journal.pone.0077638 PMID: 24204900

Alcohol Induces Sensitization to Gluten in Genetically Susceptible

PLoS One

Conclusions

Alcohol related cerebellar degeneration may, in genetically susceptible individuals, induce sensitization to gluten. Such sensitization may result from a primary cerebellar insult, but a more systemic effect is also possible. The duration and amount of exposure to alcohol may not be the only factors responsible for the cerebellar insult.

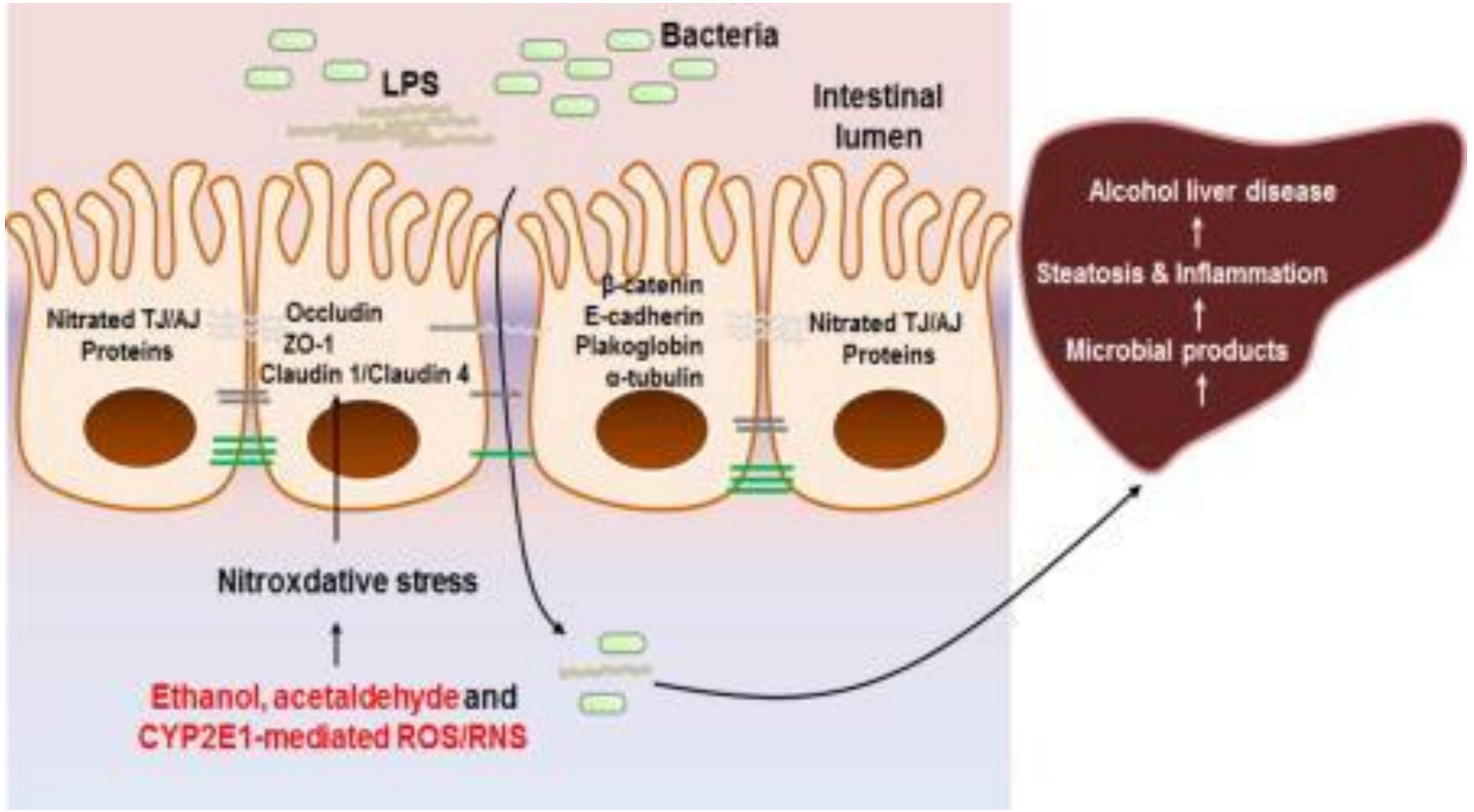
Abstract

Go to:

Background

The mechanisms of cerebellar degeneration attributed to prolonged and excessive alcohol intake remain unclear. Additional or even alternative causes of cerebellar degeneration are often overlooked in suspected cases of alcohol-related ataxia. The objectives of this study were two fold: (1) to investigate the prevalence of gluten-related serological markers in patients with alcohol-related ataxia and; (2) to compare the pattern of brain involvement on magnetic resonance imaging between patients with alcohol and gluten ataxias.

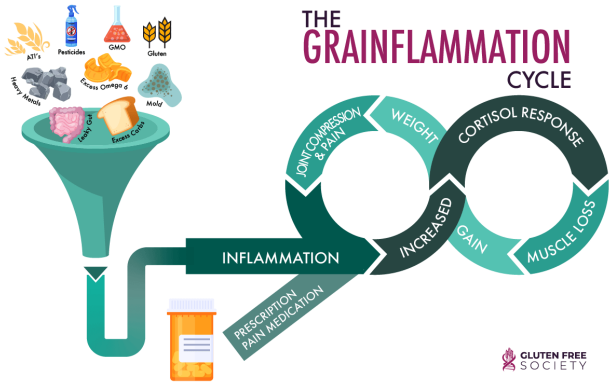
Alcohol & Leaky Gut…



"Heavy alcohol intake is also known to cause gut leakiness, contributing to increased endotoxemia and inflammatory tissue damage in the liver and brain [1-4]. Various pathological conditions, such as HIV infection [5-7], obesity [8], and burn injury [9], are known to increase gut leakiness and endotoxemia. In addition, binge alcohol [10] and nonalcoholic substances such as high fat diets [11] and fructose [12] can stimulate gut leakiness, leading to elevated serum endotoxin and liver inflammation."

Image from:

Cho, Young-Eun et al. "Apoptosis of enterocytes and nitration of junctional complex proteins promote alcohol-induced gut leakiness and liver injury." *Journal of hepatology* vol. 69,1 (2018): 142-153.



Alcohol + Circadian Disruption…

Image & Concept from: Forsyth, Christopher B et al. “Circadian rhythms, alcohol and gut interactions.” *Alcohol (Fayetteville, N.Y.)* vol. 49,4 (2015): 389-98.

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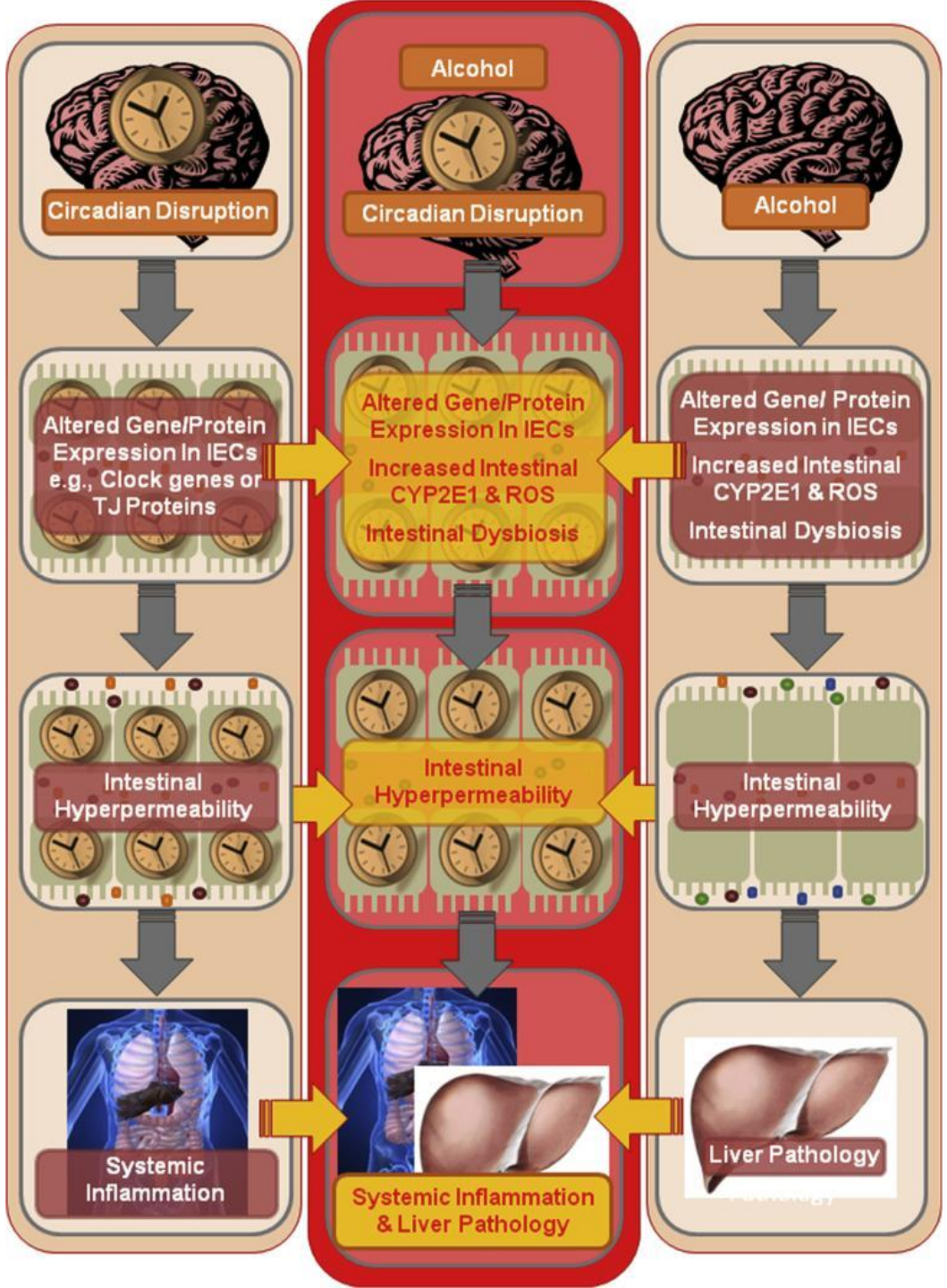

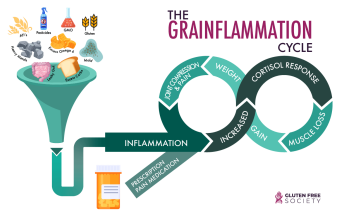

Fructose Causes Leaky Gut…

› Hepatology. 2021 Jun;73(6):2180-2195. doi: 10.1002/hep.30652. Epub 2019 May 31.

Fructose Promotes Leaky Gut, Endotoxemia, and Liver Fibrosis Through Ethanol-Inducible Cytochrome P450-2E1-Mediated Oxidative and Nitrative Stress

Young-Eun Cho [1 2], Do-Kyun Kim [3], Wonhyo Seo [4], Bin Gao [4], Seong-Ho Yoo [5], Byoung-Joon Song [1]

Affiliations + expand

PMID: 30959577 PMCID: PMC6783321 (available on 2022-06-01) DOI: 10.1002/hep.30652

Abstract

Fructose intake is known to induce obesity, insulin resistance, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD). We aimed to evaluate the effects of fructose drinking on gut leakiness, endotoxemia, and NAFLD and study the underlying mechanisms in rats, mice, and T84 colon cells. Levels of ileum junctional proteins, oxidative stress markers, and apoptosis-related proteins in rodents, T84 colonic cells, and human ileums were determined by immunoblotting, immunoprecipitation, and immunofluorescence analyses. Fructose drinking caused microbiome change, leaky gut, and hepatic inflammation/fibrosis with increased levels of nitroxidative stress marker proteins cytochrome P450-2E1 (CYP2E1), inducible nitric oxide synthase, and nitrated proteins in small intestine and liver of rodents. Fructose drinking significantly elevated plasma bacterial endotoxin levels, likely resulting from decreased levels of intestinal tight junction (TJ) proteins (zonula occludens 1, occludin, claudin-1, and claudin-4), adherent junction (AJ) proteins (β-catenin and E-cadherin), and desmosome plakoglobin, along with α-tubulin, in wild-type rodents, but not in fructose-exposed Cyp2e1-null mice. Consistently, decreased intestinal TJ/AJ proteins and increased hepatic inflammation with fibrosis were observed in autopsied obese people compared to lean individuals. Furthermore, histological and biochemical analyses showed markedly elevated hepatic fibrosis marker proteins in fructose-exposed rats compared to controls. Immunoprecipitation followed by immunoblot analyses revealed that intestinal TJ proteins were nitrated and ubiquitinated, leading to their decreased levels in fructose-exposed rats. Conclusion: These results showed that fructose intake causes protein nitration of intestinal TJ and AJ proteins, resulting in increased gut leakiness, endotoxemia, and steatohepatitis with liver fibrosis, at least partly, through a CYP2E1-dependent manner.

Review › J Nutr Biochem. 2009 Sep;20(9):657-62. doi: 10.1016/j.jnutbio.2009.05.006.

Dietary fructose and intestinal barrier: potential risk factor in the pathogenesis of nonalcoholic fatty liver disease

Astrid Spruss [1], Ina Bergheim

Affiliations + expand

PMID: 19679262 DOI: 10.1016/j.jnutbio.2009.05.006

Abstract

Worldwide, not only the prevalence of obesity has increased dramatically throughout the last three decades but also the incidences of co-morbid conditions such as diabetes type 2 and liver disease have increased. The 'hepatic manifestation of the metabolic syndrome' is called nonalcoholic fatty liver disease (NAFLD) and comprises a wide spectrum of stages of liver disease ranging from simple steatosis to liver cirrhosis. NAFLD of different stages is found in approximately 30% of adults and approximately 20% in the US population. Not just a general overnutrition but also an elevated intake of certain macronutrients such as fat and carbohydrates and herein particularly fructose has been claimed to be risk factors for the development for NAFLD; however, the etiology of this disease is still unknown. The present review outlines some of the potential mechanisms associated with the development of NAFLD and fructose intake with a particular focus on the role of the intestinal barrier functions.

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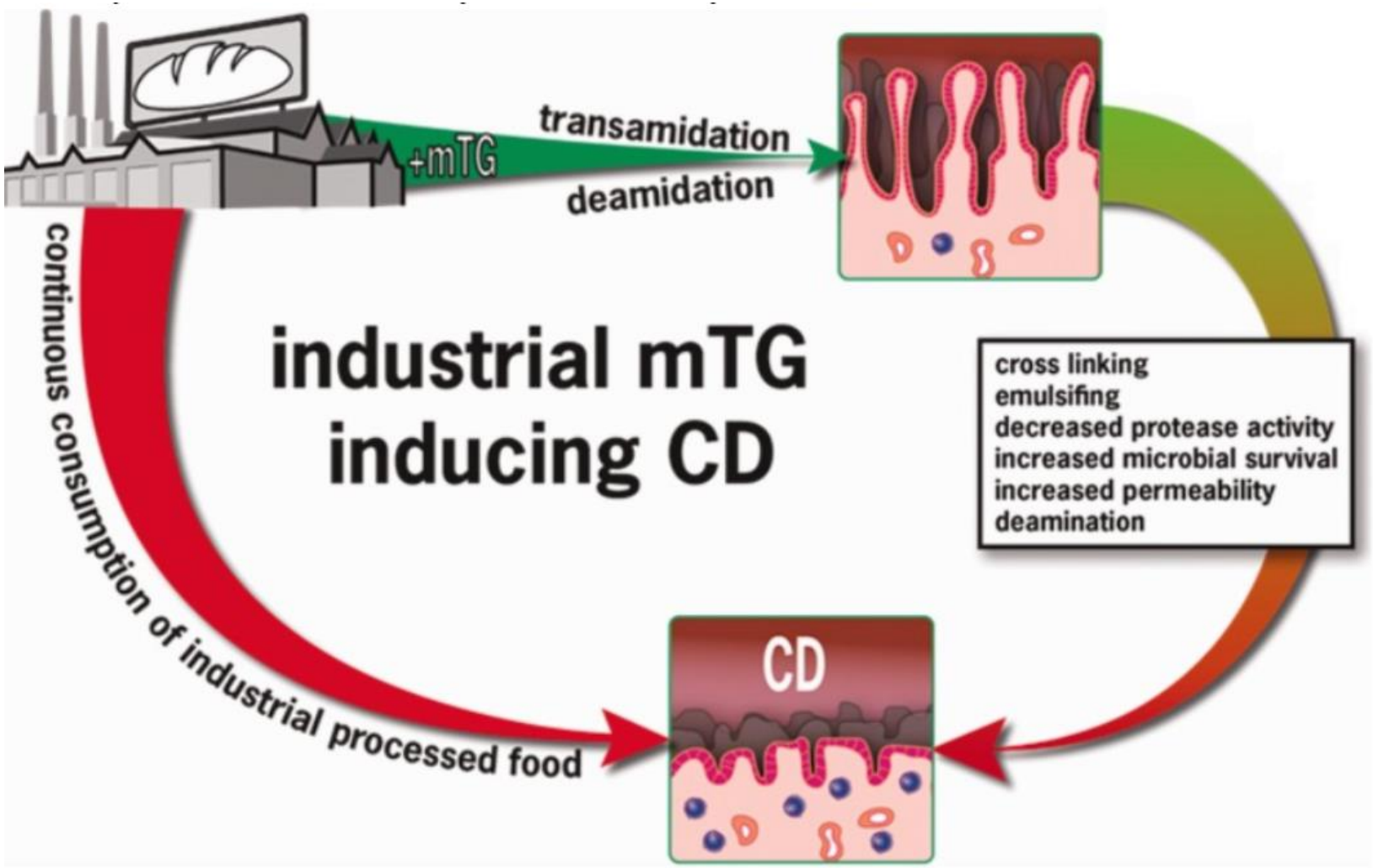

Image from: *Nutrition Reviews*. 73(8), 544-552

Glyphosate…

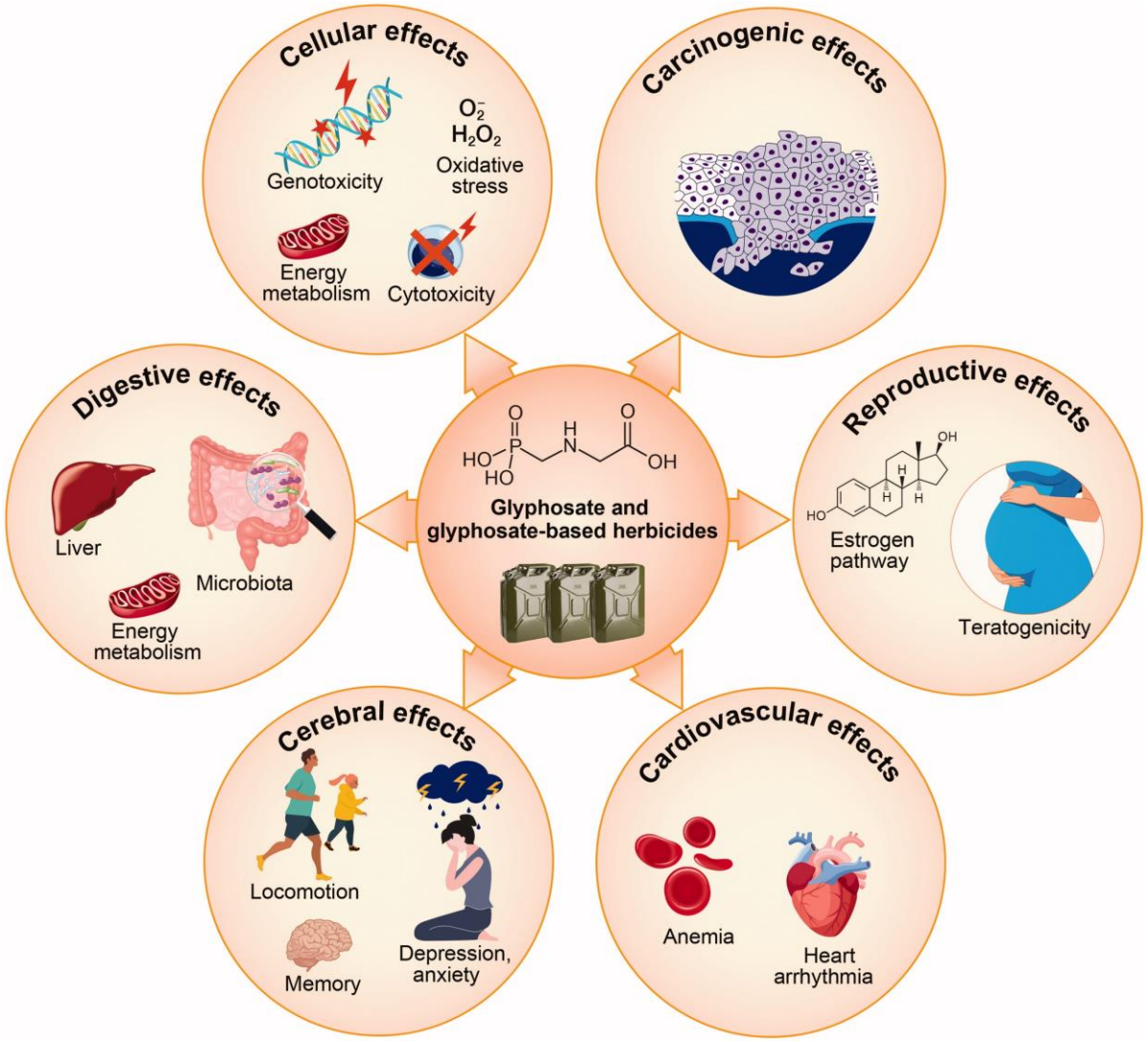

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Image from: Cindy Peillex & Martin Pelletier (2020) The impact and toxicity of glyphosate and glyphosate-based herbicides on health and immunity, *Journal of Immunotoxicology*, 17:1, 163-174.

Journal of Organic Systems, 9(2), 2014

ORIGINAL PAPER

Genetically engineered crops, glyphosate and the deterioration of health in the United States of America

Nancy L. Swanson[1], Andre Leu[2]*, Jon Abrahamson[3] and Bradley Wallet[4]

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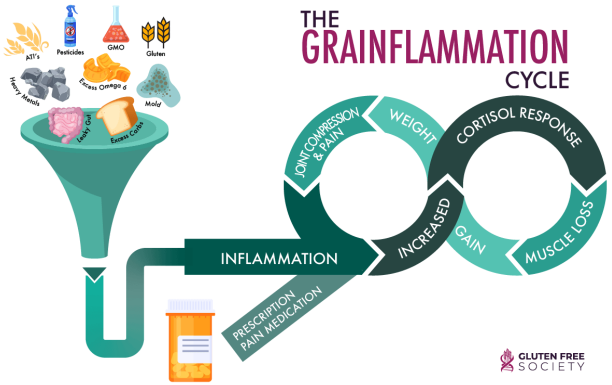
[2] *International Federation of Organic Agricultural Movements, Bonn, Germany*
[3] *Abacus Enterprises, Lummi Island, WA, USA*
[4] *Crustal Imaging Facility, Conoco Phillips School of Geology and Geophysics, University of Oklahoma, USA*
* *Corresponding author: andreleu.al@gmail.com*

Abstract

A huge increase in the incidence and prevalence of chronic diseases has been reported in the United States (US) over the last 20 years. Similar increases have been seen globally. The herbicide glyphosate was introduced in 1974 and its use is accelerating with the advent of herbicide-tolerant genetically engineered (GE) crops. Evidence is mounting that glyphosate interferes with many metabolic processes in plants and animals and glyphosate residues have been detected in both. Glyphosate disrupts the endocrine system and the balance of gut bacteria, it damages DNA and is a driver of mutations that lead to cancer.

In the present study, US government databases were searched for GE crop data, glyphosate application data and disease epidemiological data. Correlation analyses were then performed on a total of 22 diseases in these time-series data sets. The Pearson correlation coefficients are highly significant ($< 10^{-5}$) between glyphosate applications and hypertension (R = 0.923), stroke (R = 0.925), diabetes prevalence (R = 0.971), diabetes incidence (R = 0.935), obesity (R = 0.962), lipoprotein metabolism disorder (R = 0.973), Alzheimer's (R = 0.917), senile dementia (R = 0.994), Parkinson's (R = 0.875), multiple sclerosis (R = 0.828), autism (R = 0.989), inflammatory bowel disease (R = 0.938), intestinal infections (R = 0.974), end stage renal disease (R = 0.975), acute kidney failure (R = 0.978), cancers of the thyroid (R = 0.988), liver (R = 0.960), bladder (R = 0.981), pancreas (R = 0.918), kidney (R = 0.973) and myeloid leukaemia (R = 0.878).

The Pearson correlation coefficients are highly significant ($< 10^{-4}$) between the percentage of GE corn and soy planted in the US and hypertension (R = 0.961), stroke (R = 0.983), diabetes prevalence (R = 0.983), diabetes incidence (R = 0.955), obesity (R = 0.962), lipoprotein metabolism disorder (R = 0.955), Alzheimer's (R = 0.937), Parkinson's (R = 0.952), multiple sclerosis (R = 0.876), hepatitis C (R = 0.946), end stage renal disease (R = 0.958), acute kidney failure (R = 0.967), cancers of the thyroid (R = 0.938), liver (R = 0.911), bladder (R = 0.945), pancreas (R = 0.841), kidney (R = 0.940) and myeloid leukaemia (R = 0.889). The significance and strength of the correlations show that the effects of glyphosate and GE crops on human health should be further investigated.



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The Majority of Serotonin & Dopamine are Produced in the Gut

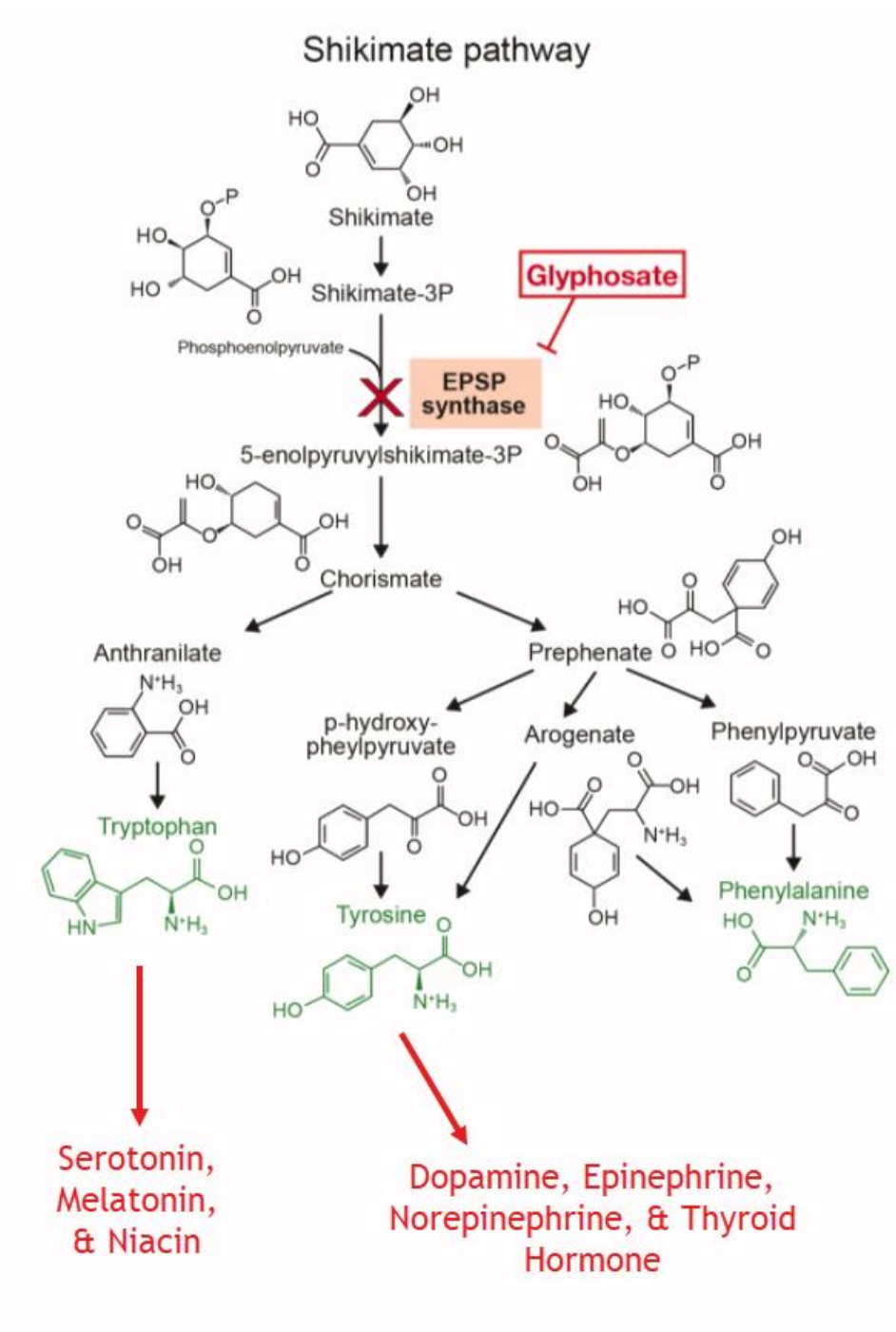


Image modified from: Cindy Peillex & Martin Pelletier (2020) The impact and toxicity of glyphosate and glyphosate-based herbicides on health and immunity, *Journal of Immunotoxicology*, 17:1, 163-174.

Glyphosate Causes Reduced Nutrients in Plants*

- Calcium
- Potassium
- Magnesium
- Zinc
- Copper
- Boron
- Iron
- Manganese
- Sulphur
- Phosphorus

*Martinez, D.A., Loening, U.E. & Graham, M.C. Impacts of glyphosate-based herbicides on disease resistance and health of crops: a review. *Environ Sci Eur* **30,** 2 (2018).

frontiers in Cellular and Infection Microbiology

REVIEW
published: 26 February 2018
doi: 10.3389/fcimb.2018.00060

Mycotoxin: Its Impact on Gut Health and Microbiota

*Winnie-Pui-Pui Liew and Sabran Mohd-Redzwan**

Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

Mycotoxins and gut health

Upon ingestion of contaminated food or feed, the GI tract is particularly affected by mycotoxin. Generally, intestinal barrier in the GI tract functions as a filter against harmful mycotoxins. However, some mycotoxins have been found to exert their detrimental effects in the GI tract. For example, mycotoxins can alter the normal intestinal functions such as barrier function and nutrient absorption. Some mycotoxins also affect the histomorphology of intestine. The impacts of mycotoxins include trichothecenes, zearalenone, fumonisins, ochratoxins, and AFs on general and gut health will be comprehensively reviewed.

Review > J Toxicol Environ Health B Crit Rev. 2017;20(5):249-275.
doi: 10.1080/10937404.2017.1326071. Epub 2017 Jun 21.

Impact of mycotoxins on the intestine: are mucus and microbiota new targets?

Hervé Robert [1], Delphine Payros [1], Philippe Pinton [1], Vassilia Théodorou [1], Muriel Mercier-Bonin [1], Isabelle P Oswald [1]

Affiliations + expand

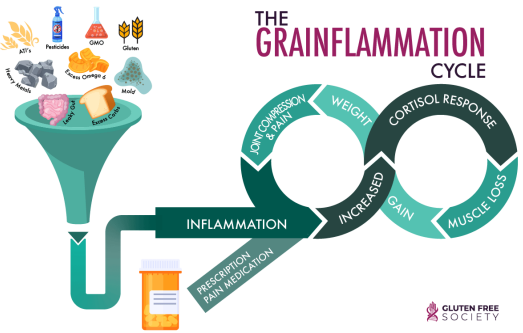
PMID: 28636450 DOI: 10.1080/10937404.2017.1326071

Abstract

There is an increasing awareness of the deleterious effects attributed to mycotoxins during their fate within the gut, particularly for deoxynivalenol (DON), zearalenone (ZEN), ochratoxin A (OTA), fumonisin B1 (FB1), aflatoxin B1 (AFB1), and patulin (PAT). Evidence indicates that disruption of the epithelial barrier is well established. However, intestinal barrier function on its luminal side involves two other partners, mucus and microbiota, which have rarely been considered in the context of mycotoxin exposure. The current review aimed at providing a summary of DON, ZEN, OTA, FB1, AFB1, and PAT effects on intestinal barrier function, with special focus on mucus and microbiota. DON, ZEN, OTA, FB1, AFB1, and PAT are known to markedly affect epithelial cell integrity and functions. Regarding mucus, DON is the most documentated mycotoxin. In vivo, toxicological impact of DON generally has only been assessed through goblet cell number. Evaluation of the mycotoxins/mucus interplay considering other indicators such as composition, thickness, and penetrability of mucus, mucin O-glycosylation thus warrants further attention. With respect to microbiota, few short-term studies to date have been reported indicating deleterious effects. However, long-term exposure to mycotoxins may also produce significant changes in microbiota composition and metabolic activity, which requires further experimentation. In conclusion, mucus and microbiota are key targets for dietary mycotoxins although assessment of induced effects is preliminary. A significant research effort is now underway to determine the adverse consequences of mycotoxins on mucus and microbiota considered as individual but also as tightly connected gut players.

microorganisms

MDPI



Review

Mucus: An Underestimated Gut Target for Environmental Pollutants and Food Additives

Kévin Gillois, Mathilde Lévêque, Vassilia Théodorou, Hervé Robert and Muriel Mercier-Bonin *

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Received: 26 May 2018; Accepted: 14 June 2018; Published: 15 June 2018

Abstract: Synthetic chemicals (environmental pollutants, food additives) are widely used for many industrial purposes and consumer-related applications, which implies, through manufactured products, diet, and environment, a repeated exposure of the general population with growing concern regarding health disorders. The gastrointestinal tract is the first physical and biological barrier against these compounds, and thus their first target. Mounting evidence indicates that the gut microbiota represents a major player in the toxicity of environmental pollutants and food additives; however, little is known on the toxicological relevance of the mucus/pollutant interplay, even though mucus is increasingly recognized as essential in gut homeostasis. Here, we aimed at describing how environmental pollutants (heavy metals, pesticides, and other persistent organic pollutants) and food additives (emulsifiers, nanomaterials) might interact with mucus and mucus-related microbial species; that is, "mucophilic" bacteria such as mucus degraders. This review highlights that intestinal mucus, either directly or through its crosstalk with the gut microbiota, is a key, yet underestimated gut player that must be considered for better risk assessment and management of environmental pollution.

GLUTEN FREE SOCIETY

Top 6 Reasons Prescription Drugs are Dispensed…

1. Pain
2. Cholesterol
3. Blood Pressure
4. Hypothyroid
5. Acid Reflux
6. Antibiotics

GLUTEN FREE SOCIETY

Source: *Prevention Magazine*
Natural Alternatives To The Top 10 Most Prescribed Drugs
By Holly C. Corbett

REVIEW article
Front. Microbiol. | https://doi.org/10.3389/fmicb.2015.01543

Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances

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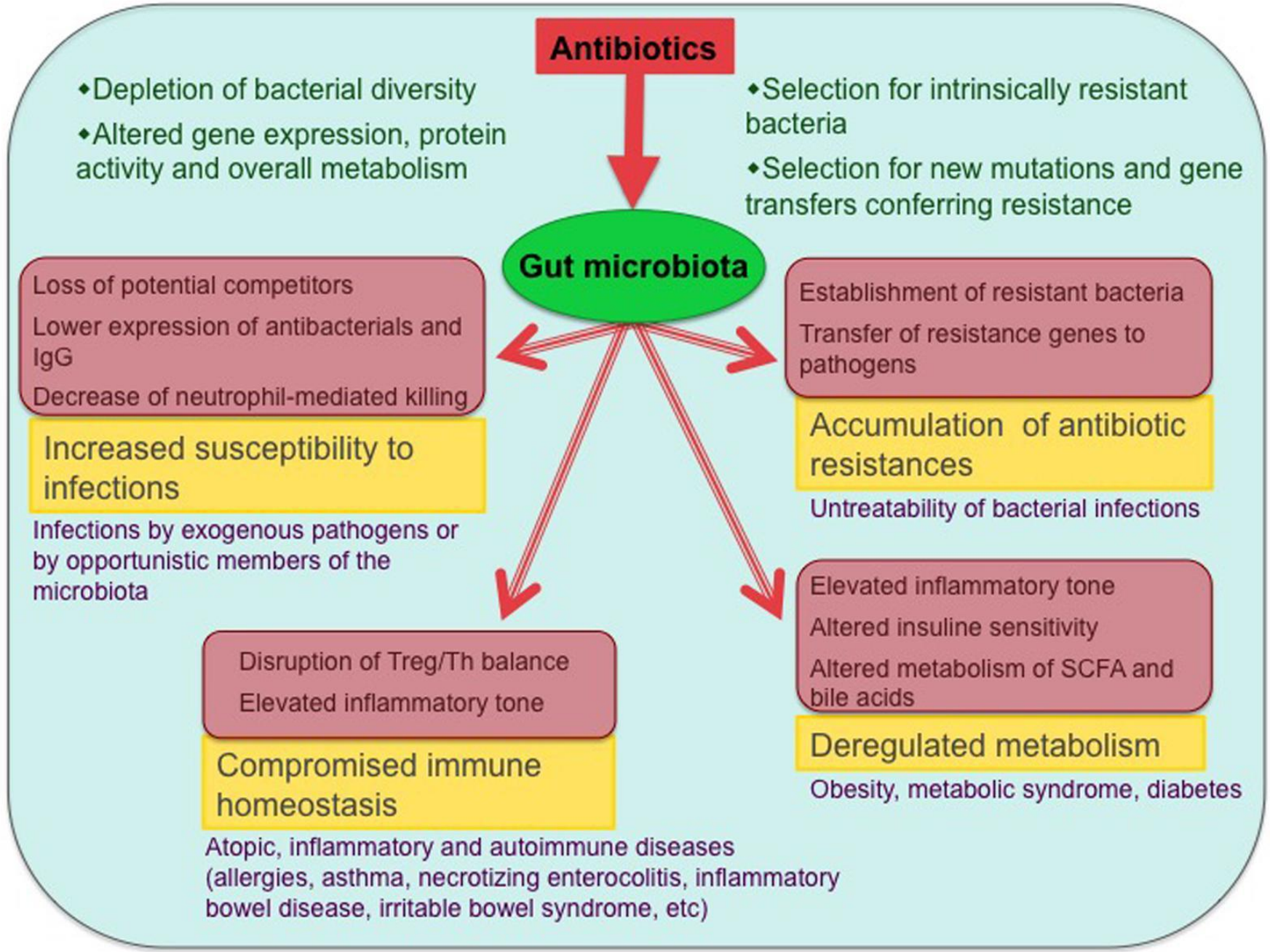
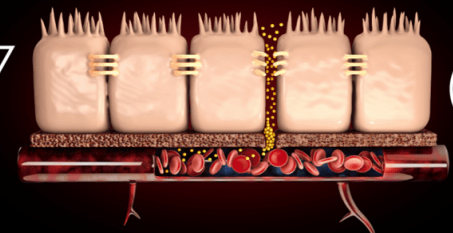
[1]Unitat Mixta d'Investigació en Genòmica i Salut, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO)-Salud Pública/Institut Cavanilles de Biodiversitat i Biologia Evolutiva, Universitat de València, València, Spain
[2]Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública, Madrid, Spain



LEAKY GUT



How Food Allergies & Sensitivities Cause Leaky Gut

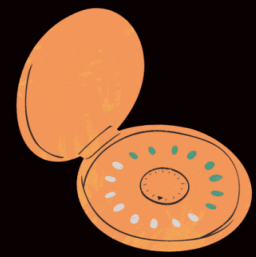
- Histamine Release
- Immune Antibody Release
- Release of Cytokines
- Activation of Toll Like Receptors
- Disruption of Zonulin

Medications That Contribute to Leaky Gut

- NSAIDs (nonsteroidal anti-inflammatory drugs)
- Birth control pills
- Antibiotics
- Immunosuppressants
- Corticosteroids
- Antacids

NSAIDS and Leaky Gut

- Direct Damage to Mucosal Lining of Stomach & Intestine
- Metabolites From Liver Breakdown Oxidize Gut Cells
- Deplete Vitamin C & Iron



Leaky Gut and Birth Control Pills

Vitamin B6
Vitamin B12
Folate
Calcium
Magnesium
Vitamin C
Vitamin E

GLUTEN FREE SOCIETY

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The Effects of Steroids Upon the Gastrointestinal Tract*

HUGH E. BLACK

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ABSTRACT

The steroid hormones and bile acids are important to digestive tract structure and function. Glucocorticoids administered during pregnancy have been shown to induce cleft palate in the offspring in several species. Postnatally, a significant rise in corticosterone during week 3 in the rat coincides with profound morphological and biochemical changes in the small intestine toward the adult state. Exogenous glucocorticoids given suckling rats leads to precocious development of these changes. In the adult, glucocorticoids increase brush border enzyme levels, while adrenal insufficiency decreases mucosal weight, enzyme activity, and absorptive functions. Water and sodium absorption and potassium excretion are enhanced in both small and large intestine. The jejunum, through its sense of food, provides the entraining signal that governs corticosterone rhythm. In the stomach, high doses of glucocorticoids inhibit prostaglandin biosynthesis, thereby inhibiting the gastric alkaline response and producing severe gastric lesions. However, in man, peptic ulcer disease is not clearly associated with glucocorticoid therapy. Exacerbation of subclinical intestinal infections and perforative lesions have been observed in both animals and man given glucocorticoids. The female sex hormone estrogen, when given to rats, stimulates intestinal enzyme levels and facilitates absorption. Progesterone inhibits both circular and longitudinal smooth muscle contractile activity. Virtually the entire pool of bile acids is found in the enterohepatic circulation. The dihydroxy secondary bile acids, regardless of their conjugation states, are physiologically and morphologically more damaging to mucosal cell membranes than are the trihydroxy primary bile acids.

Review > J Gastroenterol. 2009;44 Suppl 19:23-9. doi: 10.1007/s00535-008-2266-6. Epub 2009 Jan 16.

Intestinal permeability in the pathogenesis of NSAID-induced enteropathy

Ingvar Bjarnason [1], Ken Takeuchi

Affiliations + expand

PMID: 19148789 DOI: 10.1007/s00535-008-2266-6

Abstract

Background: The pathogenesis of nonsteroidal antiinflammatory drug (NSAID)-induced small bowel disease suggests that increased intestinal permeability is the central mechanism that translates biochemical damage to tissue damage. The purpose of this review is to summarize studies on the effect of NSAIDs to increase intestinal permeability in humans and methods for limiting this effect.

Methods: A Medline search was made for papers that described measurements of increased intestinal permeability in humans.

Results: Virtually all studies agree that all conventional NSAIDs increase intestinal permeability in the human within 24 h of ingestion and that this is equally evident when they are taken long term. Various methods have been tried to limit the damage. The most promising agents are coadministration of synthetic prostaglandins, micronutrients, pre-NSAIDs, and COX-2 selective agents. However, their efficacy in preventing the development of NSAID enteropathy in the long term has not been studied in detail, and, in the case of COX-2 selective agents, small bowel damage is comparable to that which is seen with conventional NSAIDs.

Conclusions: NSAID enteropathy is associated with significant morbidity and occasionally mortality. There are no proven effective ways of preventing this damage. Because increased intestinal permeability appears to be a central mechanism in the pathogenesis of NSAID enteropathy, it becomes a potential therapeutic target for prevention. At present there are a number of ways to limit the increased permeability, but additional studies are required to assess if this approach reduces the prevalence and severity of NSAID enteropathy.

Review

The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents

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Abstract

Most anti-inflammatory drugs have been associated with an increased risk of serious upper gastrointestinal complications. Epidemiological studies have estimated the magnitude of the risk for specific anti-inflammatory drugs. The risk of upper gastrointestinal tract bleeding or perforation increases around twofold with use of oral steroids or low dose aspirin, and increases around fourfold with use of nonaspirin nonsteroidal anti-inflammatory drugs. Acetaminophen at daily doses of 2000 mg and higher has also been associated with an increased risk. Overall, the risk is dose dependent and is greater with more than one anti-inflammatory drug taken simultaneously. Hence, whenever possible, anti-inflammatory drugs should be given in monotherapy and at the lowest effective dose in order to reduce the risk of serious upper gastrointestinal complications.

Special Article

Psychotherapy and Psychosomatics

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The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature

André F. Carvalho[a] Manu S. Sharma[c] André R. Brunoni[b] Eduard Vieta[e]
Giovanni A. Fava[d, f]

Key Words

Antidepressant drugs · Selective serotonin reuptake inhibitors · Serotonin noradrenaline reuptake inhibitors · Tricyclic antidepressants · Side effects · Safety · Tolerability · Depression · Iatrogenic comorbidity · Adverse events

Abstract

Newer generation antidepressant drugs (ADs) are widely used as the first line of treatment for major depressive disorders and are considered to be safer than tricyclic agents. In this critical review, we evaluated the literature on adverse events, tolerability and safety of selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, bupropion, mirtazapine, trazodone, agomelatine, vilazodone, levomilnacipran and vortioxetine. Several side effects are transient and may disappear after a few weeks following treatment initiation, but potentially serious adverse events may persist or ensue later. They encompass gastrointestinal symptoms (nausea, diarrhea, gastric bleeding, dyspepsia), hepatotoxicity, weight gain and metabolic abnormalities, cardiovascular disturbances (heart rate, QT interval prolongation, hypertension, orthostatic hypotension), genitourinary symptoms (urinary retention, incontinence), sexual dysfunction, hyponatremia, osteoporosis and risk of fractures, bleeding, central nervous system disturbances (lowering of seizure threshold, extrapyramidal side effects, cognitive disturbances), sweating, sleep disturbances, affective disturbances (apathy, switches, paradoxical effects), ophthalmic manifestations (glaucoma, cataract) and hyperprolactinemia. At times, such adverse events may persist after drug discontinuation, yielding iatrogenic comorbidity. Other areas of concern involve suicidality, safety in overdose, discontinuation syndromes, risks during pregnancy and breast feeding, as well as risk of malignancies. Thus, the rational selection of ADs should consider the potential benefits and risks, likelihood of responsiveness to the treatment option and vulnerability to adverse events. The findings of this review should alert the physician to carefully review the appropriateness of AD prescription on an individual basis and to consider alternative treatments if available.

A.F.C. and M.S.S. contributed equally as first authors of this article.

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Drug Saf. 2016 March ; 39(3): 193–197. doi:10.1007/s40264-015-0372-y.

Risk of Inflammatory Bowel Disease with Oral Contraceptives and Menopausal Hormone Therapy: Current Evidence and Future Directions

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Abstract

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bow diseases, are archetypical inflammatory disorders of the gastrointestinal tract with rising inc worldwide. Although the role of genetic factors in disease development has been highlighte genome wide association studies, environmental risk factors likely play a pivotal role in development of CD and UC. Prior observational studies have suggested a link between exo hormone use and risk of CD and UC. Specifically, studies have shown an association betwe contraceptive use and risk of CD and menopausal hormone therapy and risk of UC. Althou exact mechanism of these associations is largely unknown, a number of hypotheses have be proposed. First, oral estrogen has been shown to modify intestinal permeability, a critical st the pathophysiology of inflammatory bowel disease. Second, exogenous hormone use throu effect on endogenous levels of hormones may enhance the development of Th1- and Th2-mediated inflammatory diseases. Lastly, recent data have linked modification in the gut microbiome to endogenous levels of androgens, which are also known to be altered with exogenous hormone use and influence the development of autoimmune diseases. This supports the intriguing hypothesis that the gut microbiome lies at the crossroads of pathways linking exogenous hormone use with innate and adaptive immunity. Future studies should therefore focus on bridging these epidemiologic findings to disease pathogenesis through comprehensive understanding of the complex interaction between exogenous hormone use, sex steroid biomarkers, genetic risk loci, and alterations in the intestinal microbial environment in the etiology of CD and UC.

Finally, there is also data linking endogenous and exogenous sex hormone to human microbiota. Available data suggest that exogenous estrogen is associated with changes in the vaginal flora, characterized by an increase in *lactobacilli* species with a concomitant decrease in vaginal infections (20–22). Oral contraceptives are also associated with an increase in certain *Candida* and *Prevotella* species in oral flora with a resultant increase in risk of periodontitis (23). In addition, recent animal data suggest that gut commensal microbes may modulate levels of endogenous testosterone, leading to development of autoimmune diseases.(24) Thus, the observed association between exogenous hormone use and endogenous testosterone and development of CD may be biologically mediated by a complex interaction between endogenous hormones, the gut microbiome, and immune function. Of note, there is also data suggesting a possible role for microvascular ischemia in etiology of CD(25, 26), which may in turn suggest that oral contraceptives through their effect in inducing microvascular ischemia increase the risk of CD.

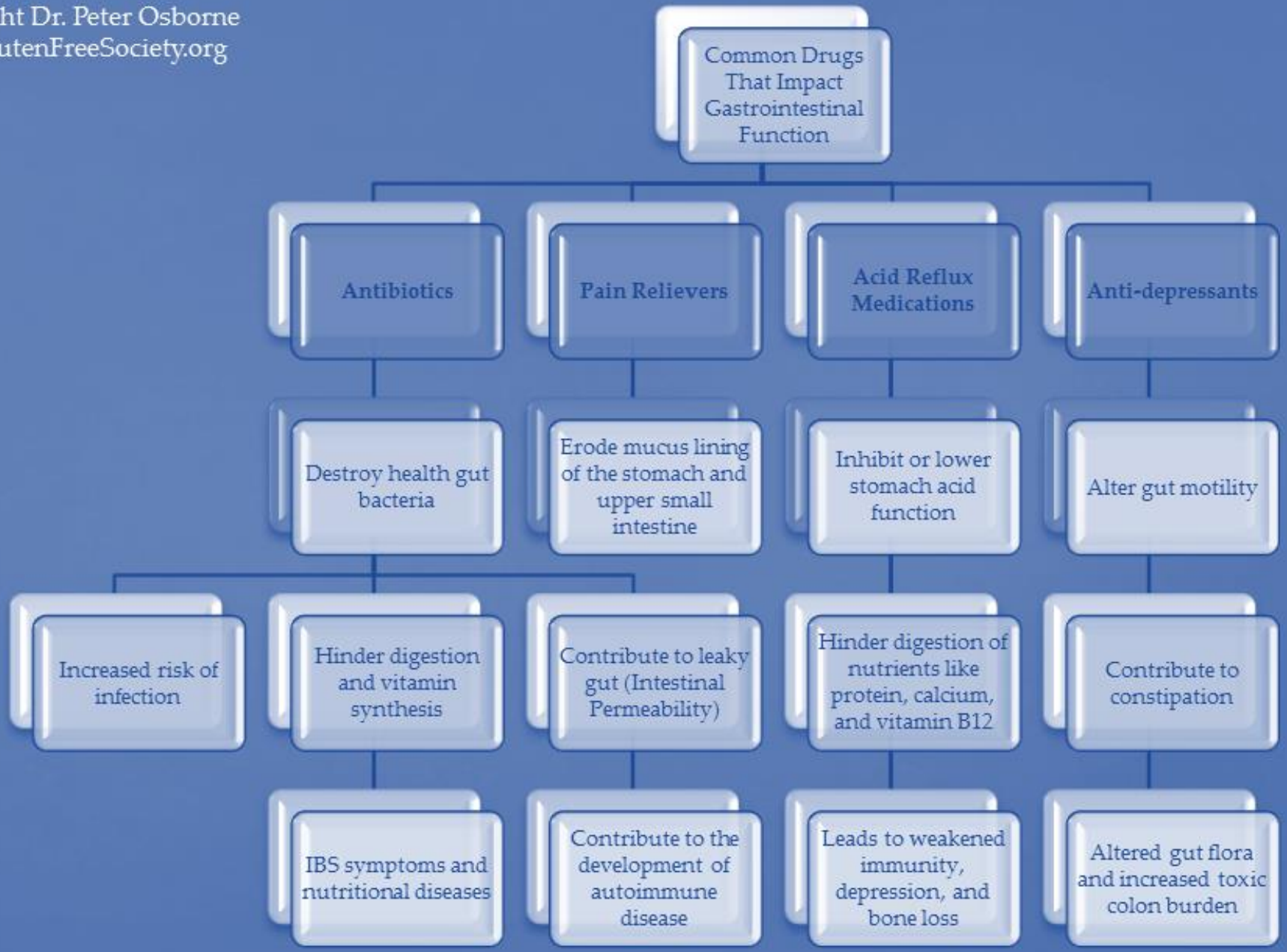
NEWS RELEASES

Researchers find antidepressants significantly increase risk of gastrointestinal, intracranial bleeding

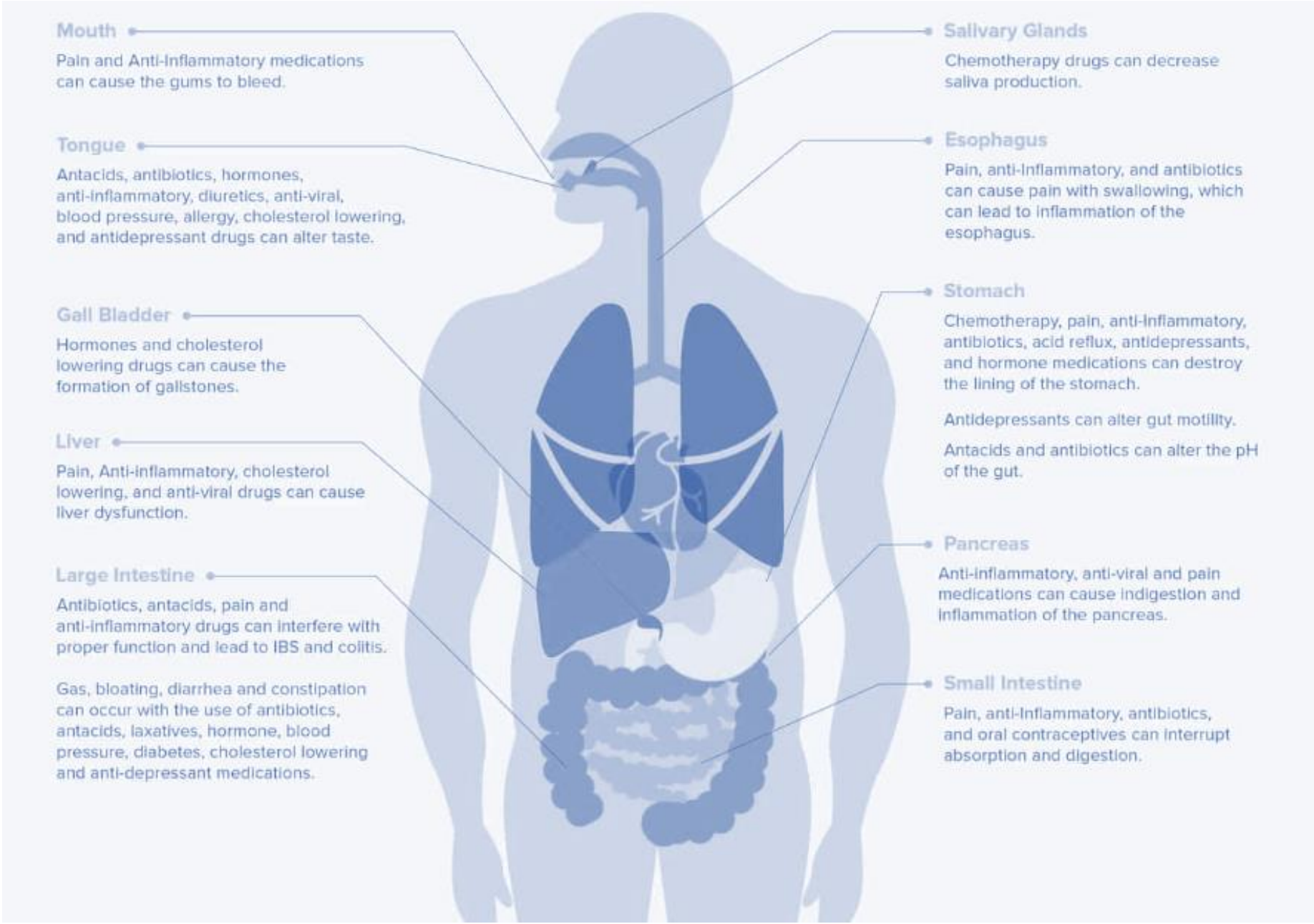
Severe bleeding up to 40% more likely for patients on SSRIs, according to review in *The Journal of the American Osteopathic Association*.

Nearly 13 percent of Americans 12 years and older take an antidepressant, and SSRIs are among the most frequently prescribed because they are relatively low-cost, effective and safe. However, they also carry risks for gastrointestinal and intracranial bleeding that compound when taken with other medications.

The most common and concerning interactions occur with nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen (Advil, Motrin) and naproxen (Aleve), anticoagulants like warfarin (Coumadin) or antiplatelet medications such as aspirin and clopidogrel (Plavix).



Medicines Can Interfere with Gut Function



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Blood Pressure Medication

- **Olmesartan is a prescription medication used to treat high blood pressure. A new study finds that the side effects of this drug can induce symptoms that mimic celiac disease…**

A research study published in *Mayo Clinic Proceedings* disclosed a very alarming discovery. Researchers have found an association between the prescription drug Olmesartan and severe gastrointestinal (GI) issues such as nausea, vomiting, diarrhea, weight loss, and electrolyte abnormalities.

Olmesartan For High Blood Pressure

“We thought these cases were celiac disease initially because their biopsies showed features very like celiac disease, such as inflammation,” said Dr. Murray. “What made them different was they didn’t have the antibodies in their blood that are typical for celiac disease.”

Be Aware...

REVIEW

Angiotensin II receptor blockers and gastrointestinal adverse events of resembling sprue-like enteropathy: a systematic review

Ayesha Kamal[1], Christopher Fain[1], Angela Park[2], Peiqi Wang[2], Eduardo Gonzalez-Velez[1], Daniel A. Leffler[3] and Susan M. Hutfless[1,4,*]

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Abstract

Background: Olmesartan, an angiotensin II receptor blocker (ARB), is associated with gastrointestinal symptoms resembling sprue-like enteropathy. Some have proposed that enteropathy may be a class effect rather than olmesartan-specific. We performed a systematic review to identify literature of sprue-like enteropathy for all ARBs.

Methods: Case reports, case series and comparative studies of ARBs were searched on PubMed and Embase databases through 21 November 2018 and then assessed.

Results: A total of 82 case reports and case series as well as 5 comparative studies, including 248 cases, were selected and analysed. The ARBs listed in the case reports were olmesartan (233 users; 94.0%), telmisartan (5 users; 2.0%), irbesartan (4 users; 1.6%), valsartan (3 users; 1.2%), losartan (2 users; 0.8%) and eprosartan (1 user; 0.4%). The periods between ARB initiation and onset of symptoms ranged from 2 weeks to 13 years. Histologic results were reported in 218 cases, in which 201 cases (92.2%) were villous atrophy and 131 cases (60.1%) were intraepithelial lymphocytosis. Human leucocyte antigen (HLA) testing was performed in 147 patients, among whom 105 (71.4%) had HLA-DQ2 or HLA-DQ8 haplotypes. Celiac-associated antibodies were tested in 169 patients, among whom 167 (98.8%) showed negative results. Gluten exclusion from the diet failed to relieve symptoms of enteropathy in 127 (97.7%) of 130 patients with information. Complete remission of symptoms after discontinuation of ARB was reported in 233 (97.4%) of the 239 patients with information. Seven cases (2.8%) reported recurrence of symptoms after restarting olmesartan; rechallenge was not reported for the non-olmesartan ARBs. The retrospective studies conducted worldwide had inconsistent study designs (e.g. differences in periods of study and case definition) and findings.

Conclusions: Although enteropathy is rare, clinicians should remain vigilant of this potential adverse event even years after medication initiation.

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Caffeine is a Drug Too…

Scand J Gastroenterol Suppl. 1999;230:35-9.

Coffee and gastrointestinal function: facts and fiction. A review.

Boekema PJ[1], Samsom M, van Berge Henegouwen GP, Smout AJ.

Author information

Abstract

BACKGROUND: Effects of coffee on the gastrointestinal system have been suggested by patients and the lay press, while doctors tend to discourage its consumption in some diseases.

METHODS: The literature on the effects of coffee and caffeine on the gastrointestinal system is reviewed with emphasis on gastrointestinal function.

RESULTS: Although often mentioned as a cause of dyspeptic symptoms, no association between coffee and dyspepsia is found. Heartburn is the most frequently reported symptom after coffee drinking. It is demonstrated that coffee promotes gastro-oesophageal reflux. Coffee stimulates gastrin release and gastric acid secretion, but studies on the effect on lower oesophageal sphincter pressure yield conflicting results. Coffee also prolongs the adaptive relaxation of the proximal stomach, suggesting that it might slow gastric emptying. However, other studies indicate that coffee does not affect gastric emptying or small bowel transit. Coffee induces cholecystokinin release and gallbladder contraction, which may explain why patients with symptomatic gallstones often avoid drinking coffee. Coffee increases rectosigmoid motor activity within 4 min after ingestion in some people. Its effects on the colon are found to be comparable to those of a 1000 kCal meal. Since coffee contains no calories, and its effects on the gastrointestinal tract cannot be ascribed to its volume load, acidity or osmolality, it must have pharmacological effects. Caffeine cannot solely account for these gastrointestinal effects.

CONCLUSIONS: Coffee promotes gastro-oesophageal reflux, but is not associated with dyspepsia. Coffee stimulates gallbladder contraction and colonic motor activity.

Acta Medica (Hradec Kralove). 2004;47(4):273-5.

The impairment of gastroduodenal mucosal barrier by coffee.

Cibicková E[1], Cibicek N, Zďánský P, Kohout P.

Author information

Abstract

BACKGROUND: Even though coffee is not considered to be responsible for development of peptic ulcer, it may, however, prolong its healing by increasing acidity of gastric content. In our former work we observed a profound increase in sucrose permeability (above normal values) in healthy volunteers regularly drinking coffee for years. In literature, many factors affecting sucrose permeability have been described so far. None of them, however, studied the effect of coffee.

SUBJECTS, MATERIALS AND METHODS: 10 young asymptomatic habitual coffee drinkers were included in the study. The probands underwent SaLM test twice--first time without coffee restriction and second time after 48-hour coffee abstinence. The ingested SaLM solution comprised sucrose (25.0 g), lactulose (10.0 g), mannitol (2.0 g), xylose (2.0 g) and water (up to 100 ml). Urine was collected for five hours and the samples were analysed using gas chromatography. Results were compared with those of 8 young healthy volunteers not drinking coffee. Permeability for sucrose was significantly higher in the group of habitual coffee drinkers in comparison with non-coffee drinkers ($p < 0.01$). After 48-hour coffee abstinence sucrose excretion decreased significantly ($p < 0.05$) to a level not differing from that of non-coffee drinkers ($p = 0.54$).

CONCLUSIONS: Our results indicate that coffee may damage gastroduodenal mucosa in habitual coffee drinkers. In a time period of 48 hours the gastroduodenal mucosa is capable of a significant regeneration.

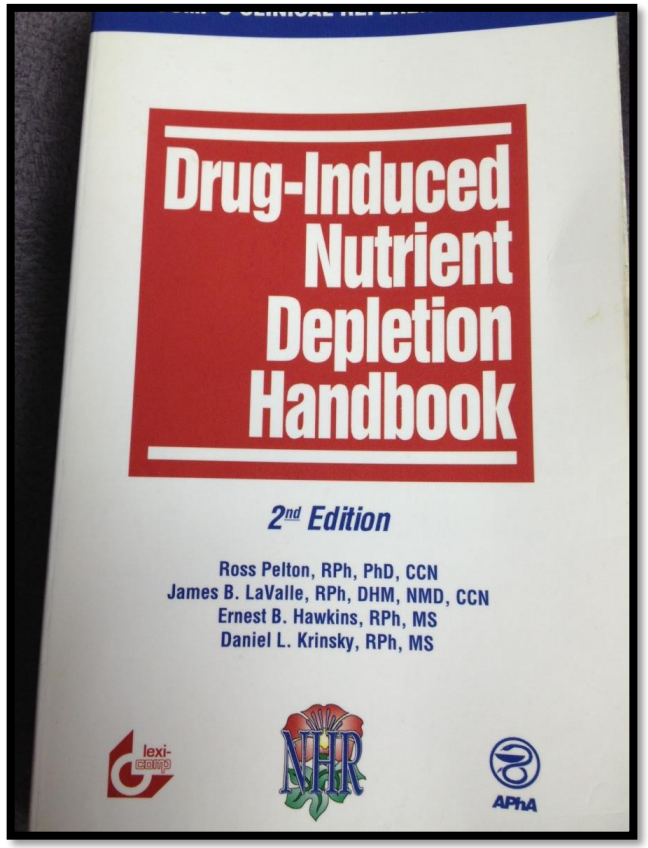
Chronic Illness Usually Means Chronic Medication Use

When meds alter gut function, we develop more problems…

More problems = more meds = more side effects = more meds…

Medicines and Nutrients

Common medications prescribed for the treatment of autoimmune disease cause vitamin and mineral deficiencies that can hinder gut recovery.



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Nutritional Deficiencies & Leaky Gut

- Vitamin D
- Vitamin A
- Vitamin C
- B Vitamins
- Magnesium
- Zinc
- Selenium
- L-Glutamine
- Short Chain Fatty Acids (Butyrate)

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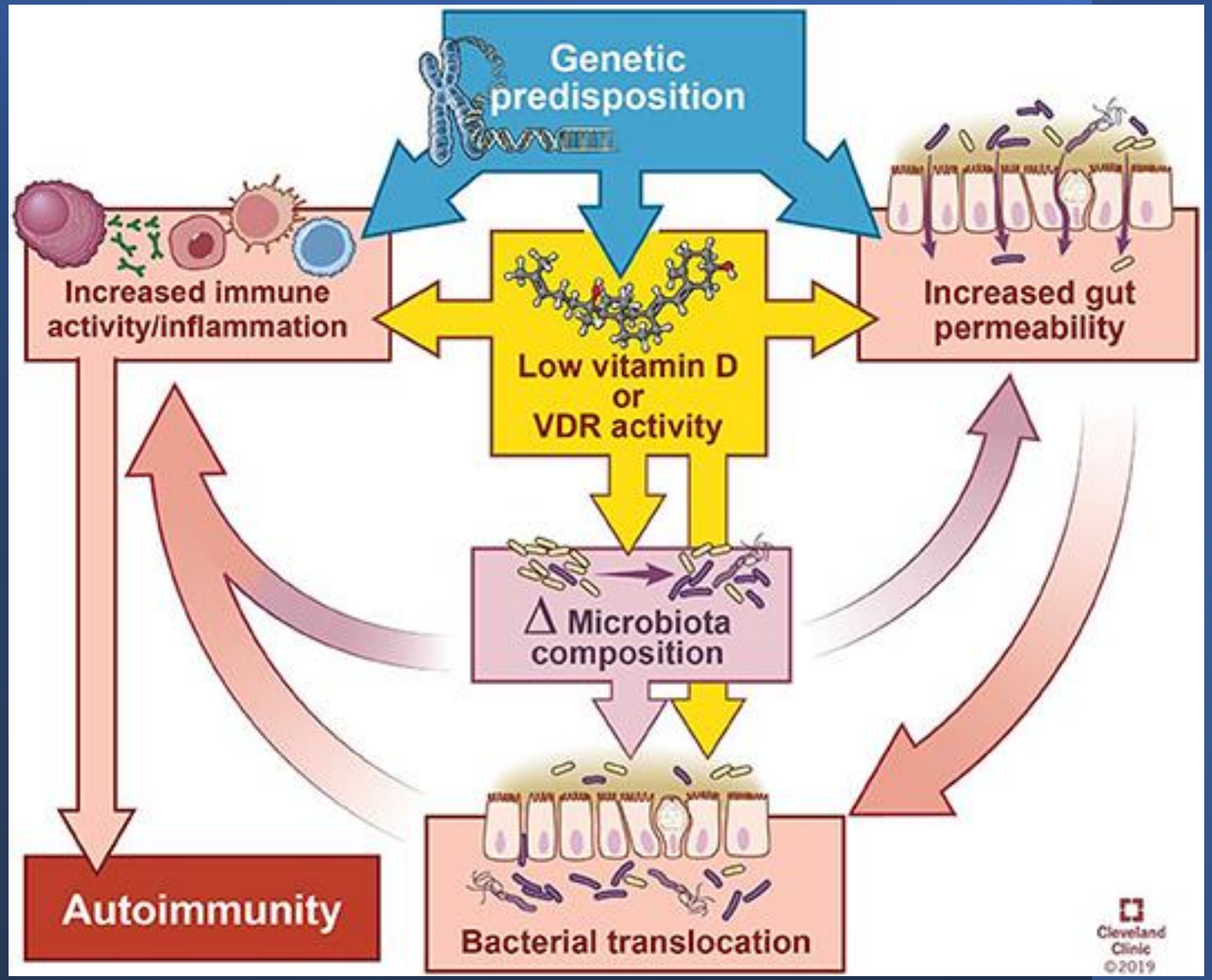
Genetic predisposition
Increased immune activity/inflammation
Low vitamin D or VDR activity
Increased gut permeability
Δ Microbiota composition
Autoimmunity
Bacterial translocation
Cleveland Clinic ©2019

Biological Psychology
Volume 138, October 2018, Pages 48-55

Effects of acute stress provocation on cortisol levels, zonulin and inflammatory markers in low- and high-stressed men

Caroline Linninge [a], Peter Jönsson [b], Hans Bolinsson [a], Gunilla Önning [c], Joakim Eriksson [d], Gerd Johansson [d], Siv Ahrné [a]

Highlights

- This study is the first to show fluctuations in gut permeability after psychosocial stress induction.
- The pro-inflammatory interleukin 6 increased with time after psychosocial stress induction, and was related to age.
- After stress induction, IL-6 and IL-8 correlated positively with zonulin.
- This study indicate, that high-stressed participants generally have higher IL-1β values than low-stressed participants.
- High-stressed participants experienced more abdominal dysfunction than low-stressed participants.

Perspective to Overcome Leaky Gut…

- Disease is the accumulation of years of damage
- **The damage is a conglomeration of environmental *bludgeoning***
- Repairing years of damage takes time.
- **Removing gluten does not repair damage, it stops one of many poisons entering the body.**
- Stopping the poison will certainly help, but it won't address all of the other environmental factors that contributed to your poor health

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Disease is Always Multifactorial

- Once you become ill, overcoming leaky gut may require more than removal of gluten/grains.
- Toxic burden impacts the function of multiple tissues in the body.
  - Liver
  - Immune Function
  - GI Tract
  - Skin
  - Lungs…

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KNOWN CAUSES OF LEAKY GUT

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www.GlutenFreeSociety.org

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- Alcohol
- Fructose
- Sleep Disruption
- Nutritional Deficiencies
- Mold Toxins
- Food Additives
- Toxic Metals

You Have to Start With Fundamentals…

- Find & Eliminate Toxic Burdens On Your Gut
- Eat real food
- Exercise
- Sleep Well
- Go Outside
- Manage Your Stress
- Filter Your Air & Water

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10 Steps to Heal Leaky Gut Syndrome Naturally

GlutenFreeSociety.org

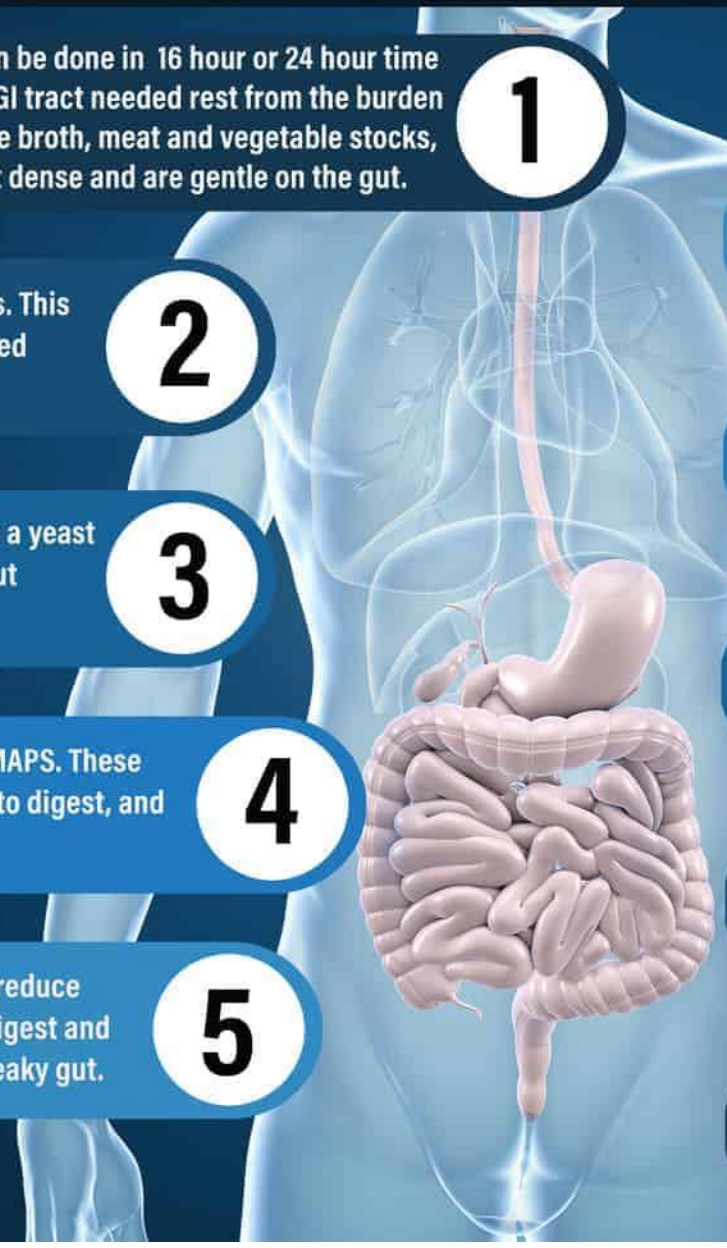
1. Consider intermittent fasting or a liquid diet. Fasting can be done in 16 hour or 24 hour time frames. Consider fasting twice per week as it gives the GI tract needed rest from the burden of digestion. If you go the liquid diet route, stick to bone broth, meat and vegetable stocks, or fresh vegetable juices. These liquids can be nutrient dense and are gentle on the gut.

2. Have your doctor test you for other hidden food allergies. This will allow you to eliminate potential sources of food based inflammation and persistent gut damage.

3. Have your doctor test you for gut infections. Often times a yeast overgrowth, a bacterial infectiont, or an imbalance in gut bacteria can contribute to persistent problems.

4. Avoid difficult to digest foods like dairy, beans and FODMAPS. These foods may be gluten free, but they are naturally harder to digest, and they can slow down your GI recovery.

5. Be wary of any medications that block stomach acid or reduce pain (NSAIDS). These medications alter your ability to digest and also strip away the GI mucosa important in regulating leaky gut.



6. Practice deep breathing exercises before eating. The act of deep breathing slows down the part of your nervous system that inhibits digestion, and activates the hormones that aid in digestion.

7. Move your body. The act of moderate walking (4-5 miles daily) stimulates the nerves that help maintain gut motility. Most people sit at a desk all day working. This sedentary lifestyle can actually contribute to a neurological slow down of your gut function.

8. Take a high quality probiotic. You will need at least 80 billion CFU's per day. Probiotics help digest your food and regulate your immune response. Many probiotics are grown on corn and cause a reaction in gluten sensitive people.

9. Consider a strong digestive enzyme formulation. Those with gluten sensitivitycommonly suffer with enzyme deficiencies, and these important proteins are necessary to break down your food and allow for proper nutrient absorption.

10. Use a supplemental source of immunoglobulins. These immune proteins are helpful in binding gut pathogens (bacteria, yeast, virus), supporting gut immune function, and supporting gut barrier function.

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Healing Fully Can Take 2-3 years

Remove the Bad

- Food Allergies
- Toxins
- Microbial Imbalances
- GI Altering medications

Replace & Repair

- Calm inflammation
- Good Bacteria
- Food & Nutrients
- Environmental Nutrients

Restore & Maintain

- Healing Phase
- Work on Building solid foundation of health
- Exercise
- Rest
- Sunshine
- Stress Management
- Positive Thoughts

Supplemental Support…

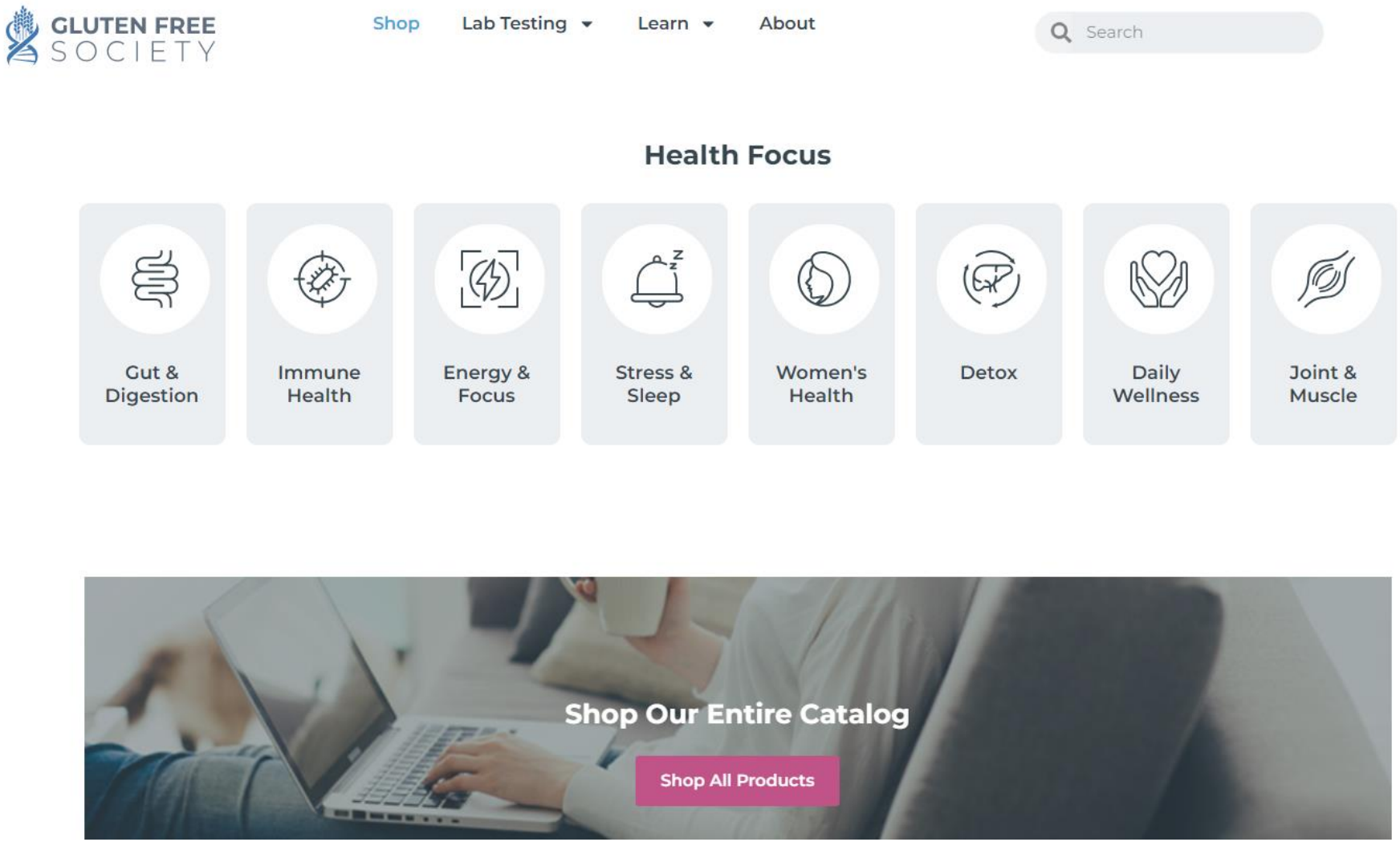
- **It is Essential to Restore Gut Motility**
  - Ultra Fiber
  - Probiotics
  - Prebiotics (Butyrate)
  - Water
  - Movement
- **Supplements to Support You on Your Journey**
  - Mucilaginous Products to Soothe the Gut
    - GI Shield
    - GI Soothe
  - Nutrients to Support Gut Energy Balance & Healthy Cell Turnover
    - L-Glutamine - doses can vary greatly (start with 1-2 grams in divided doses daily)
    - Ultra Nutrients – 2-4 caps/day
  - Supplements To Support Digestion
    - Gluten Shield®
    - Ultra Acid
    - Lipogest

Helping Support a Health Inflammation Response

- Healing Broths and organic foods
- Intermittent Fasting
- Supplement to Support You
  - Detox C Cleanse with maintenance dose of vitamin C (5-10 grams daily) Be aware that most vitamin C formulations are made from corn.
  - Vitamin D 5,000 – 10,000 IU per day plus sunshine exposure.
  - Ultra Turmeric (4-6 caps daily)
  - Ultra LGS (4-6 caps/daily)
  - Immune Shield (2 scoops/daily)
  - Ultra Biotic Defense (1 packet/day)

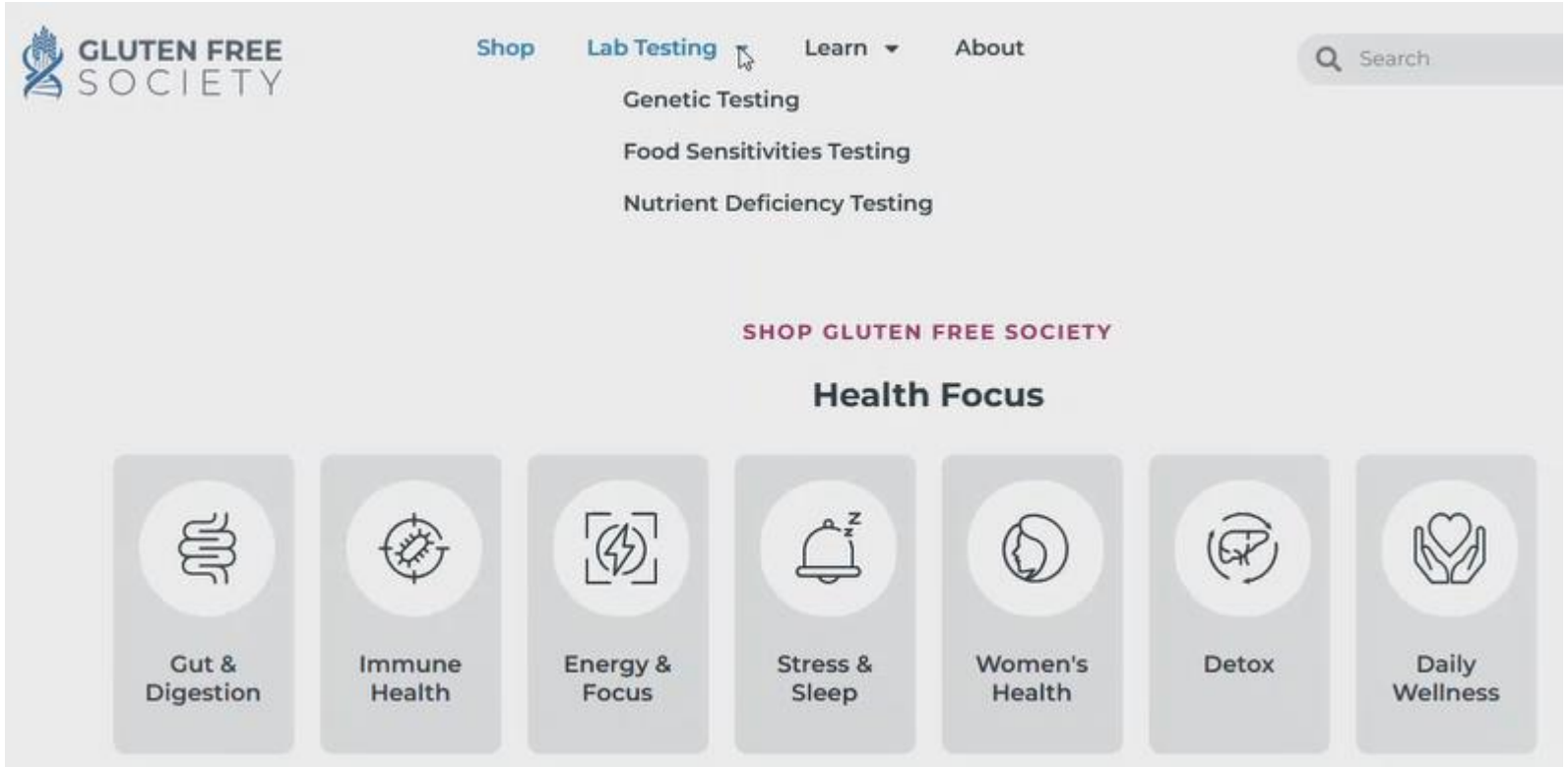
Leaky Gut Bonus

Use promo code "LEAKY" to save 15% on your order for any of the supplements listed on the two previous slides. Discount code expires 03/15/2024. You can find all supplements eligible for the discount HERE: https://www.glutenfreesociety.org/product-category/leaky-gut/



If Diet and Lifestyle Fail…

- Test for specific food exposures and REMOVE them.
- Identify nutritional deficits – correct them.
- Ask you doctor to test for and address underlying microbial imbalances



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