

The spectacular role of the human microbiome in preventing metabolic endotoxemia, the number one cause of mortality worldwide.

Kiran Krishnan
Microbiologist, Clinical Researcher





WHAT IS METABOLIC ENDOTOXEMIA?

Metabolic endotoxemia is essentially an innate immune response that becomes a sub-clinical, persistent, low-grade inflammation because of increased, circulating endotoxins. – Primarily LPS.

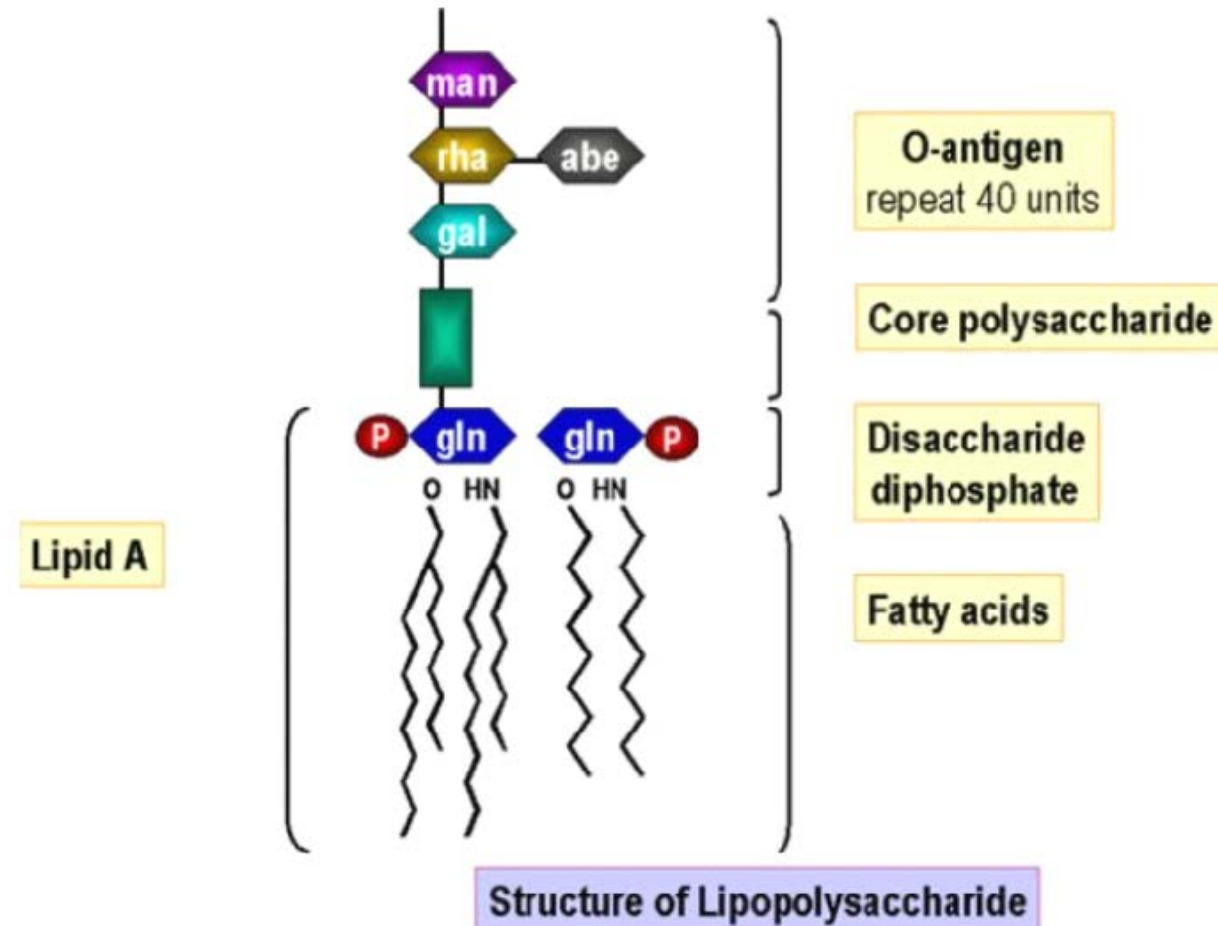
- Metabolic endotoxemia is a condition that is estimated to affect approximately 33% of the western population.
- The condition is characterized by increased serum endotoxin (typically lipopolysaccharide) concentration during the first five hours of the post-prandial period following consumption of a meal.
- Meals that are high in fat and dense in calories seem to impact the condition more so than low fat and low calorie meals.
- This increase in serum endotoxin concentration is followed by elevated inflammation that is marked by measurable increases in **interleukin-6**, **interleukin-1-alpha**, **interferon-gamma**, **triglycerides** and **post-prandial insulin**.
- Chronic metabolic endotoxemia and the associated inflammation has been shown to have significant correlation to increases in the risk of developing a variety of chronic diseases.

To date, studies support a strong correlation between metabolic endotoxemia (ME) and the increased risk or onset of conditions such as cardiovascular disease, diabetes, obesity, hypogonadism, autoimmunity and even mood disorders such as anxiety and depression.

What is endotoxin?

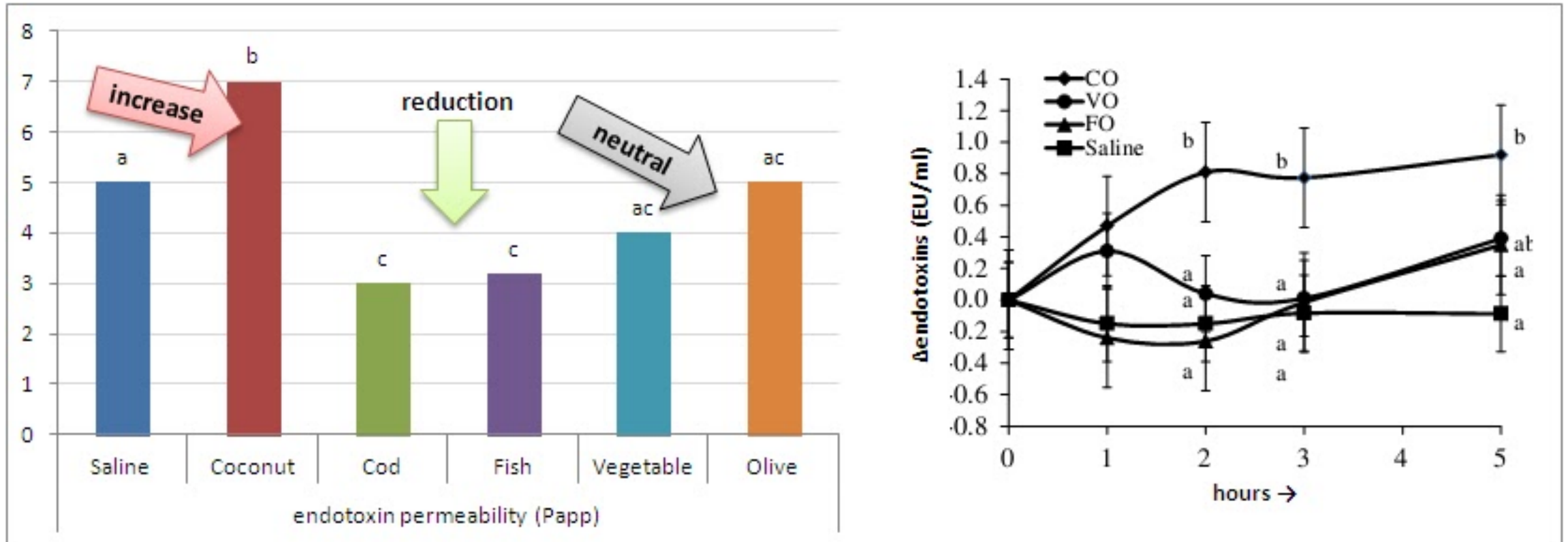
AKA lipopolysaccharide (LPS)

- Inflammatory immunogens
- Component of gram-negative bacterial outer cell wall
 - Adhesin for colonization of host
 - Diversity of antigenic strains
- Circulates at low-grade levels in healthy individuals
- Toxicity mainly mediated by the lipid-A component



<http://caltagmedsystems.blogspot.com/2013/05/uscn-specialist-elisa-kit-manufacturer.html>

TYPES OF DIETARY FATS AND ENDOTOXEMIA



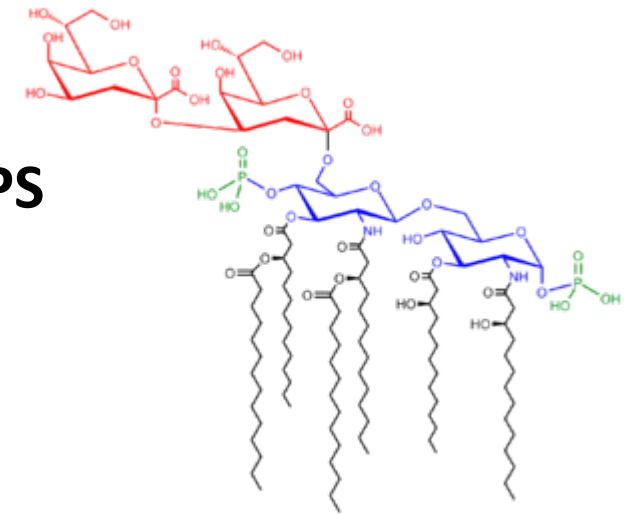
Endotoxin permeability and changes in serum endotoxin levels in the hours subsequent to the ingestion of a test meal containing either 50ml coconut (CO), vegetable (VO) and fish oil (FO) in otherwise healthy pigs (Mani. 2013).

Why does the type of fat matter?

Saturated fat (SFA) and n-3 PUFAs have opposite effects on LPS receptor, TLR4, and lipid rafts

- Lipid-A component of LPS is composed of SFA
- Endotoxin toxicity is reduced when SFA in lipid-A is substituted for n-3 PUFAs

Lee, et al. J Biol Chem. 2004;279:16971-16979



How does endotoxin enter the blood?

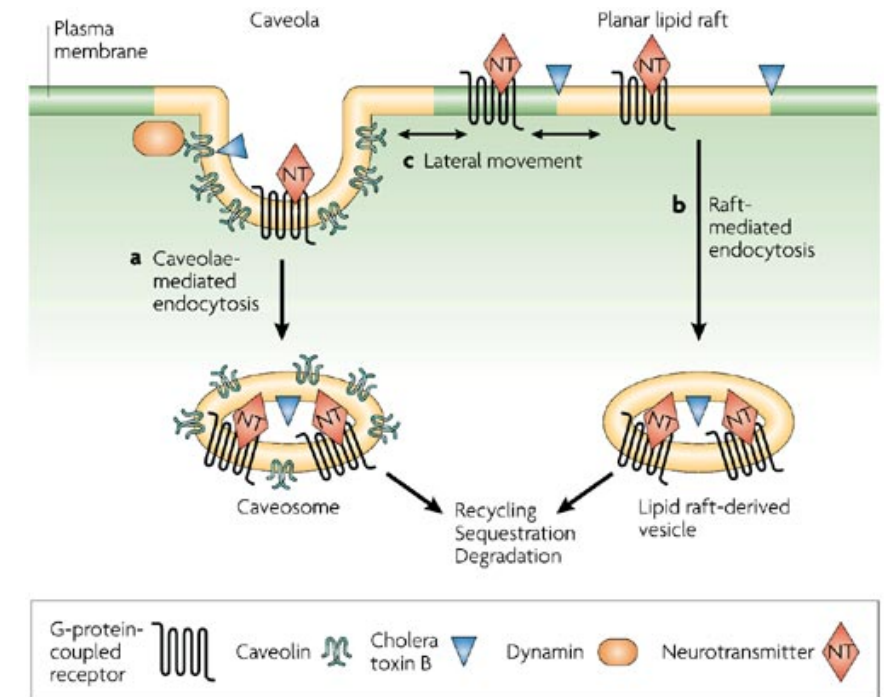
Paracellular pathways

- Via tight junctions

Transcellular pathways

- Via lipid rafts (endocytosis)
 - Rigid portion of membrane
 - Composed of cholesterol, SFA
 - Important in cell signaling

Triantafilou, et al. J Cell Sci. 2002;115:2603-2611;





IMMUNE ACTIVATION IN METABOLIC ENDOTOXEMIA

Immune activation by LPS starts with an ubiquitous Pattern-recognition receptor called TLR4

TLR4 is an important signaling protein in innate immunity and is found on the surfaces of innate immune defense cells like Macrophages and dendritic cells.

These cells also contain an important immune complex called CD14, which binds to TLR4 to facilitate the recognition of patterns on gram negative and gram positive bacteria.

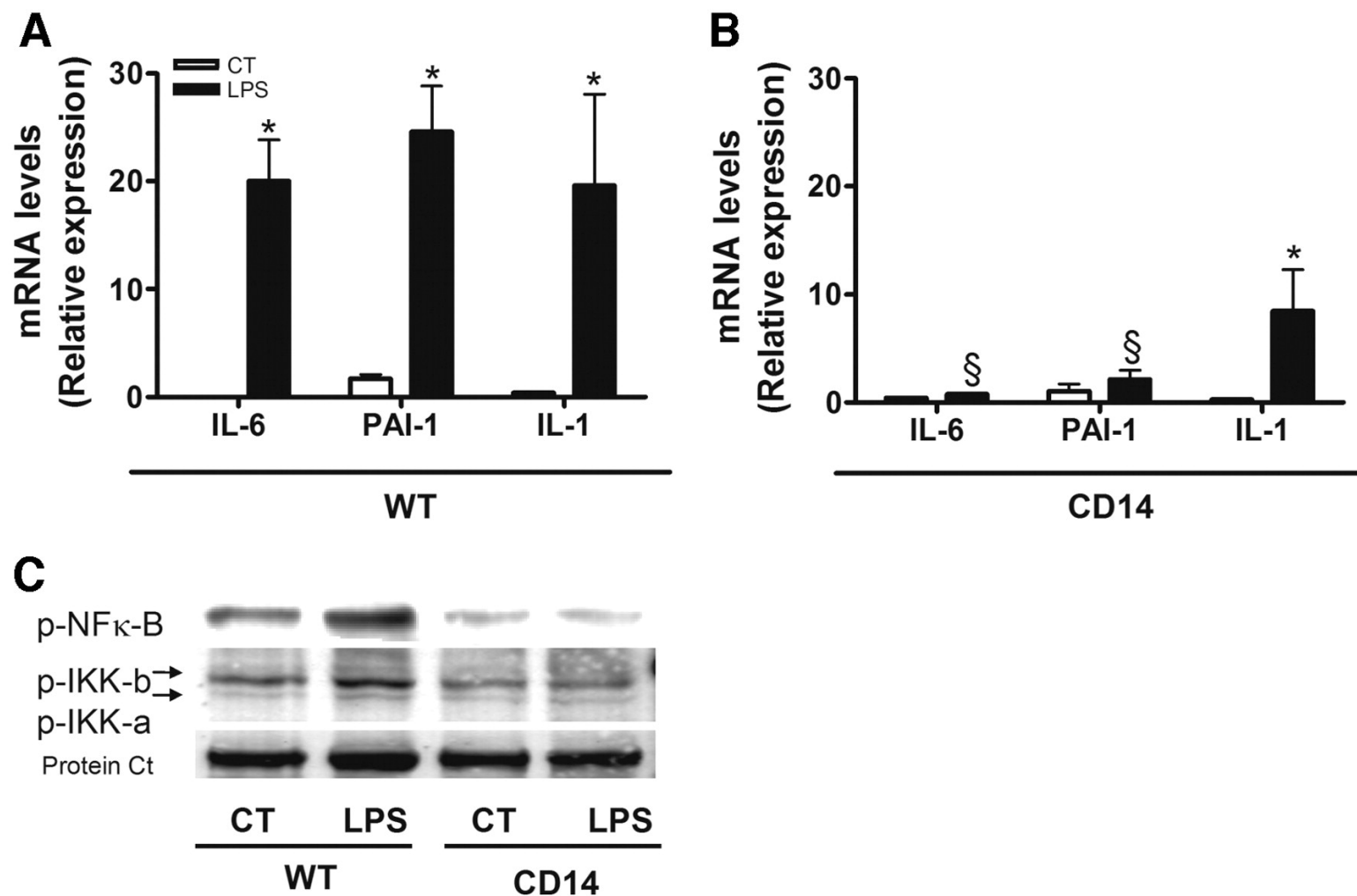
Circulating LPS gets bound by a phospholipid transfer protein called LBP, which carries LPS to the CD14-TLR complex for examination.

Once LPS-LBP has bound to the CD14-TLR complex, it initiates an immune cascade that leads to the activation of NF- κ B

The activation of NF- κ B leads to the increased expression of pro-inflammatory mediators TNF α , IL-1 β , IL-6 and MCP-1.

Innate immune cells that become activated by LPS and subsequently cause the chronic release of pro-inflammatory cytokines, exist in all parts of the body, including the blood-brain barrier.

CD14 mutant mice are protected against LPS-induced inflammation. mRNA concentrations of IL-6, PAI-1, and IL-1 in adipose tissue 3 h after a saline (control [CT]; n = 6) or an LPS (n = 6) infusion in WT (A) and CD14 mutant (B) mice. *P < 0.05 vs.



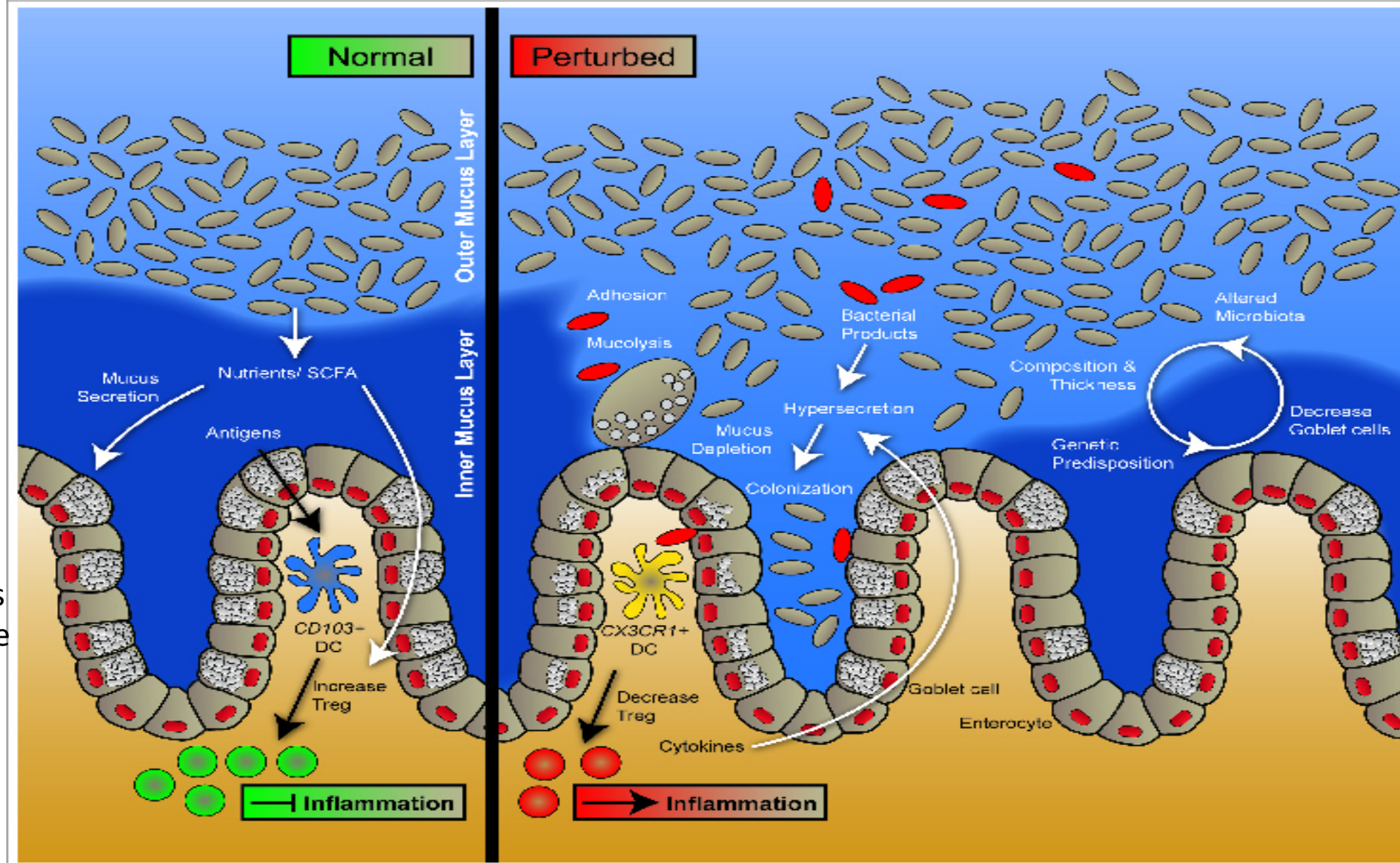
Patrice D. Cani et al. Diabetes 2007;56:1761-1772

MICROBIAL-IMMUNE-METABOLIC AXIS OF COMMUNICATION

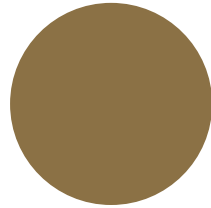
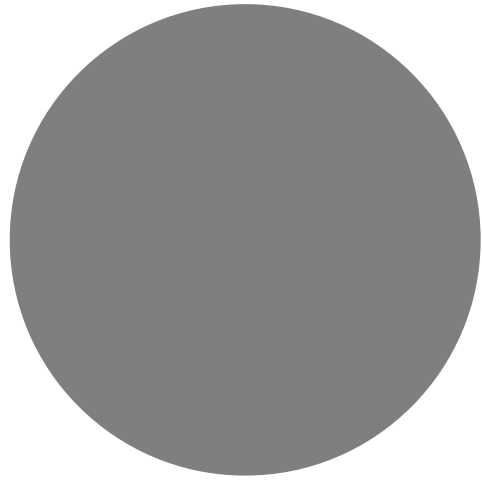


Positive Microbiome Metabolites
i.e. butyrate, acetate, indole, taurine, intactin

EIC Derived Anti-microbials:
 α -defensins, lysozyme C, phospholipases and C-type lectin



Negative Microbiome Metabolites:
i.e. Sialic acid, Succinate, mucinase



CLINICAL MANIFESTATIONS OF LPS INDUCED CHRONIC IMMUNE ACTIVATION

THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



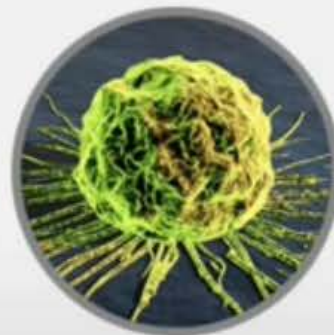
HYPERTENSION



TYPE 2 DIABETES



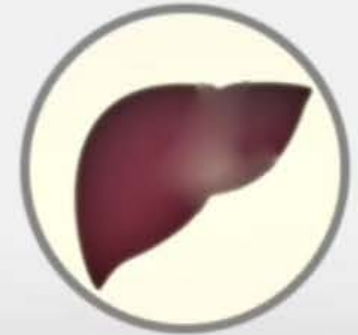
DEMENTIA



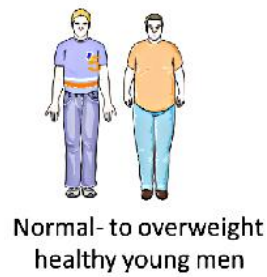
CANCER



**POLYCYSTIC
OVARIAN
SYNDROME**

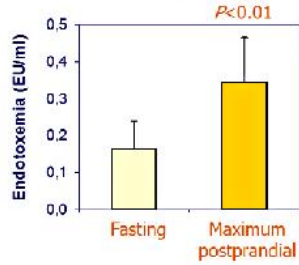


**NON-ALCOHOLIC
FATTY LIVER
DISEASE**



Normal- to overweight healthy young men

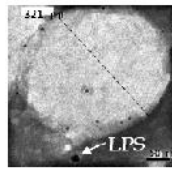
Mixed meal (33 g fat):
Banana, Bread, Jam, Fortimel® emulsion,
Margarine, Butter, Olive oil



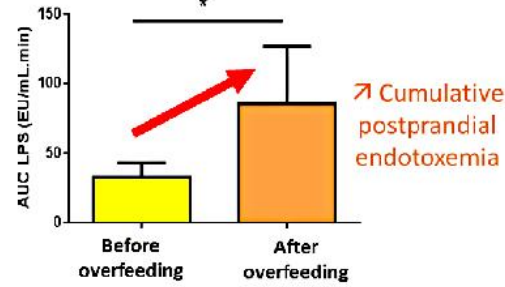
↗ Endotoxemia
↗ sCD14
↗ IL-6 (2 h)

8 weeks overfeeding
(+760 kcal/day)

LPS partly bound to chylomicrons:



Same mixed meal (33 g fat):



↗ Cumulative postprandial endotoxemia



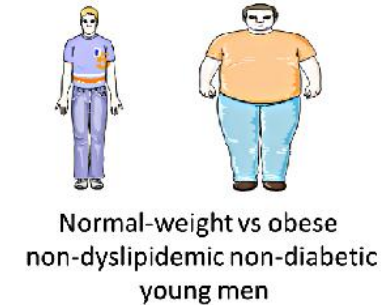
↗ Ratio LBP/sCD14 transporters

↗ Fasting IL-6 for the highest
↗ LBP/sCD14

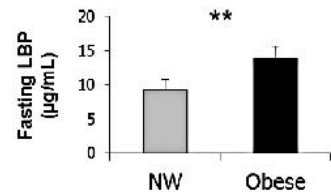
Summary of recent studies about postprandial endotoxemia in lean, overweight or obese men

(Laugerette *et al.*, [2011](#), [2014](#); Vors *et al.*, [2015](#)).

Upper panel: lean to overweight subjects were submitted to the same postprandial test before and after 8 weeks of overfeeding.



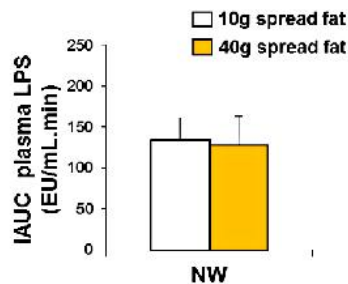
Normal-weight vs obese non-dyslipidemic non-diabetic young men



↗ Fasting LBP in obese

In entire cohort:
Correlation with postprandial IL-6

Mixed meal with 10 g or 40 g fat:
Bread, Skim milk, Anhydrous milkfat

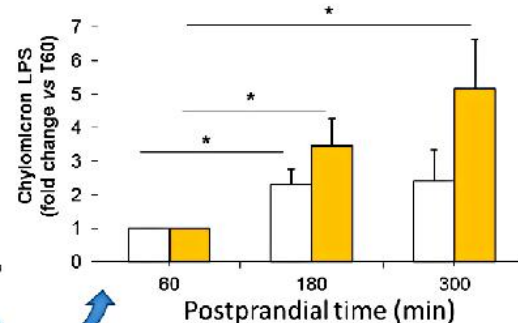


↗ Cumulative postprandial endotoxemia with meal fat content in obese

In entire cohort:
Correlation with postprandial triglyceridemia

Obese - Chylomicrons

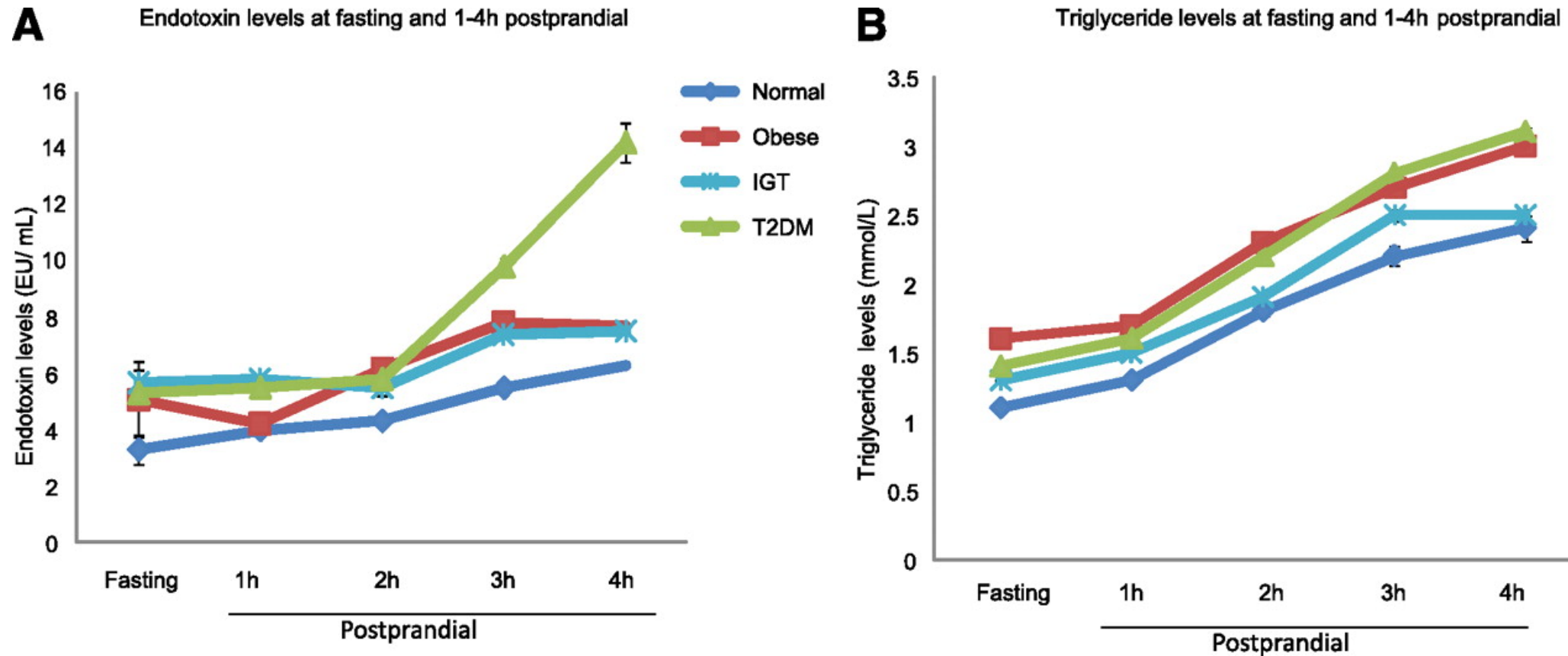
□ 10g spread fat ■ 40g spread fat



↗ Transport of LPS by chylomicrons in obese

Lower panel: lean and obese subjects were submitted to two different postprandial tests varying by the amount of fat in the meal.

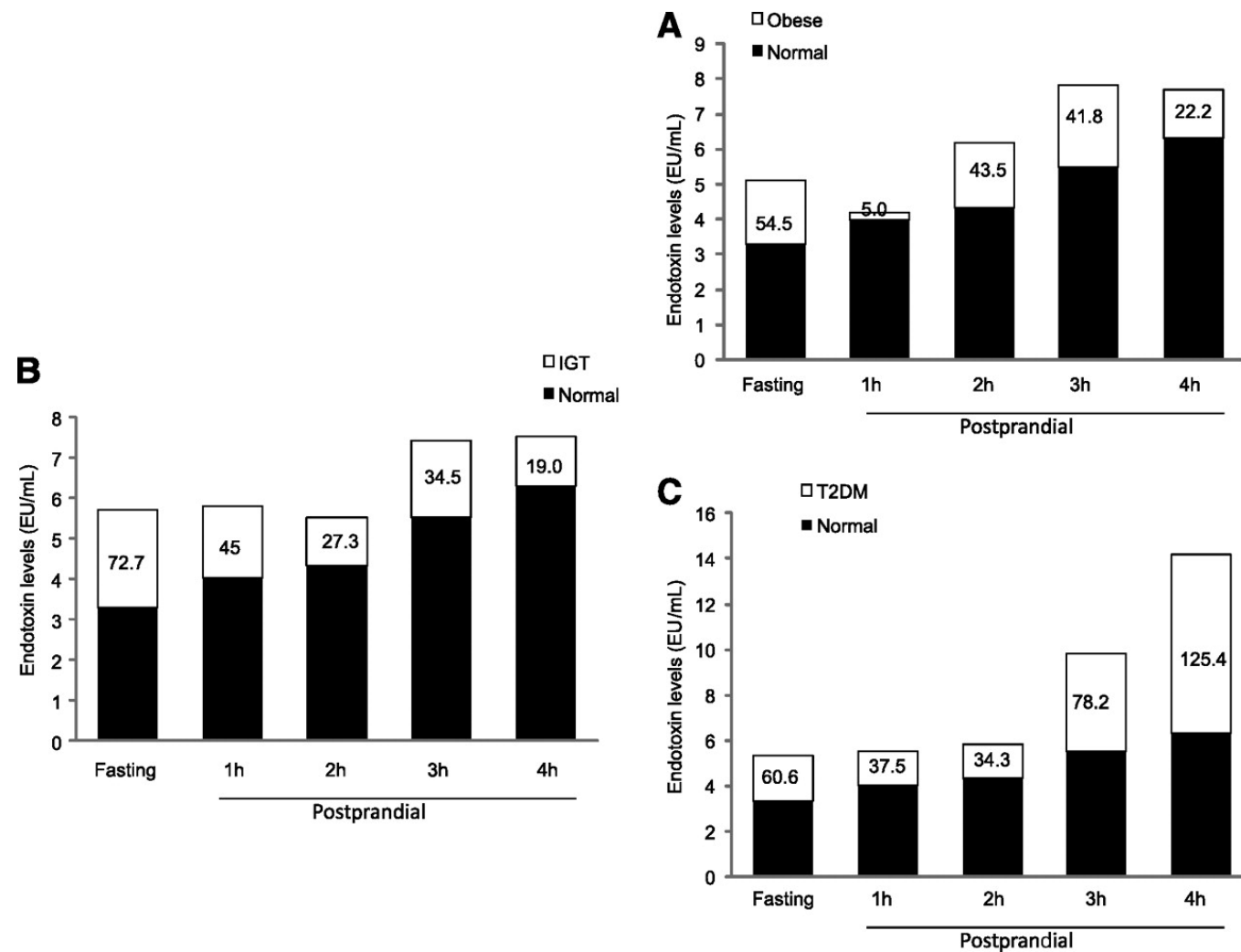
Changes in circulating endotoxin levels (A) and triglyceride levels (B) in NOC, IGT, obese, and type 2 diabetic (T2DM) subjects.



changes in circulating endotoxin levels (A) and triglyceride levels (B) in NOC, IGT (impaired glucose tolerance), obese, and type 2 diabetic (T2DM) subjects. Endotoxin and triglyceride levels were measured at baseline and then, after a high-SFA meal, at each hour postprandially over a 4-h duration. Each point on the graph represents the mean value for each cohort (\pm SEM).

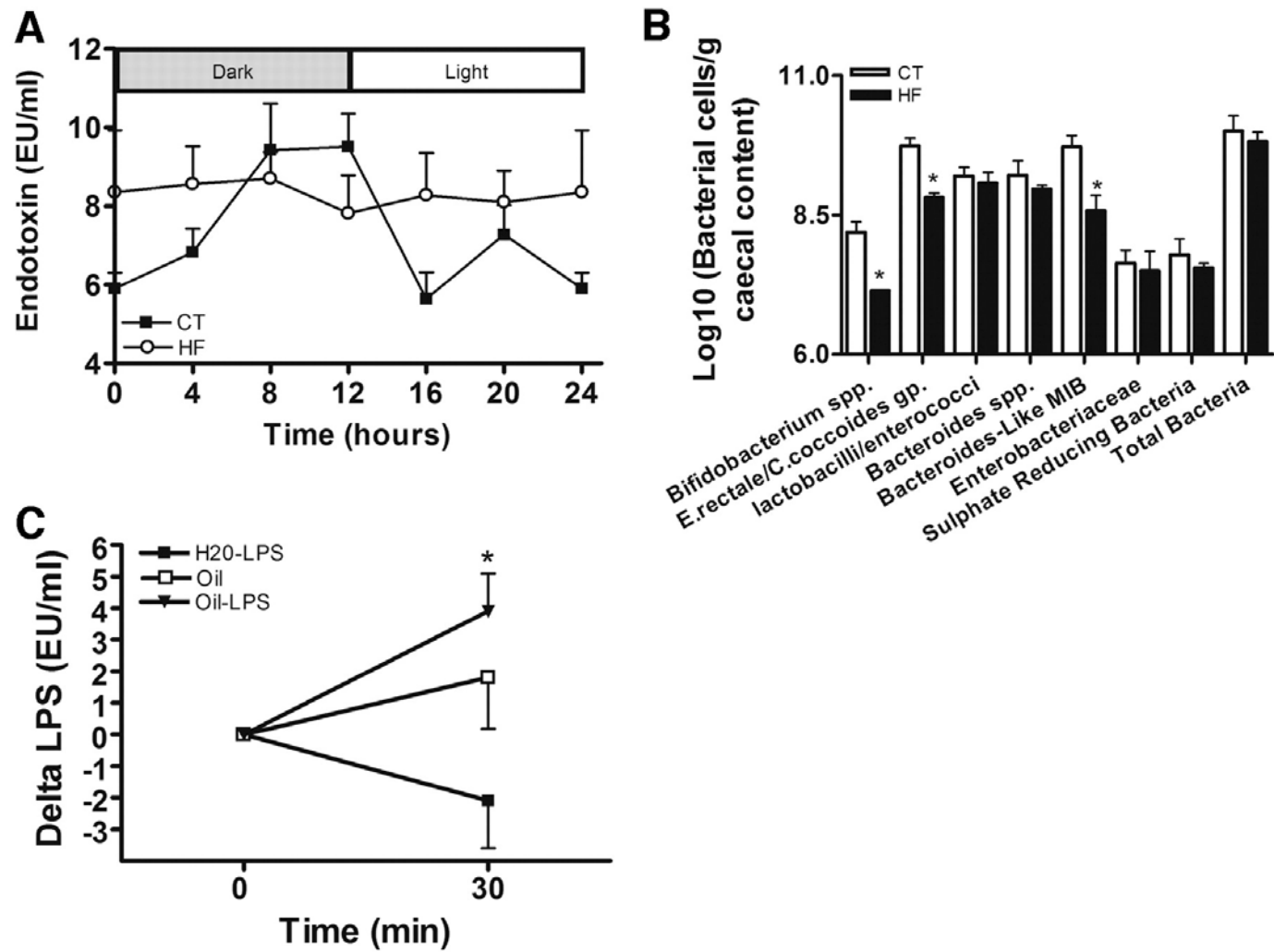
Alison L. Harte et al. *Dia Care* 2012;35:375-382

Increase in endotoxin levels between the NOC subjects and the obese (A), IGT (B), and type 2 diabetic (T2DM) (C) subjects from baseline to 4 h after a high-fat meal.



Alison L. Harte et al. Dia Care 2012;35:375-382

High-fat feeding increased endotoxemia and changed intestinal microbiota.

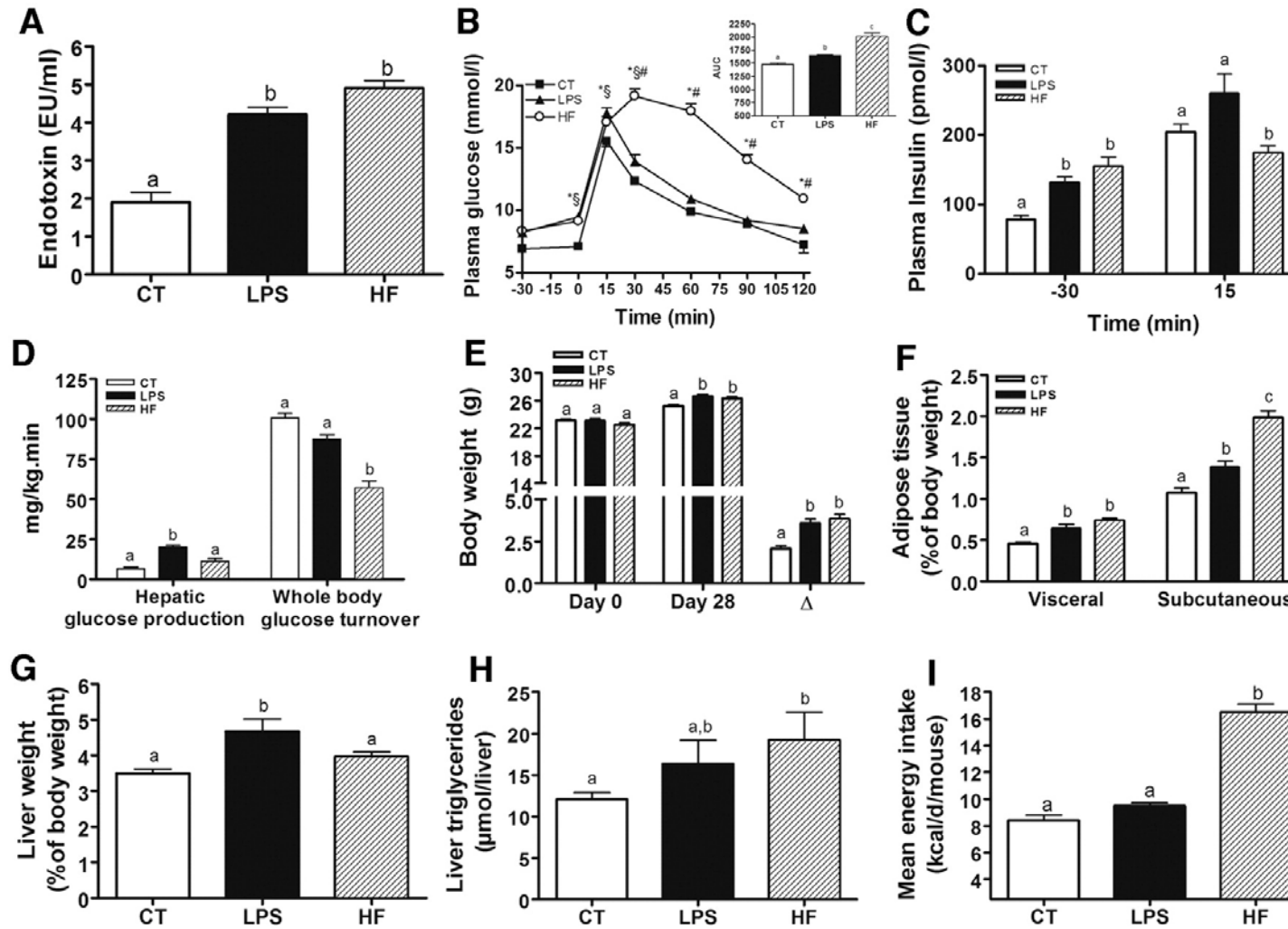


Patrice D. Cani et al. Diabetes 2007;56:1761-1772

A fluffy yellow chick is standing on a dark surface, looking at a large brown egg. A speech bubble originates from the chick, containing the text "I was here first!". The background is solid black.

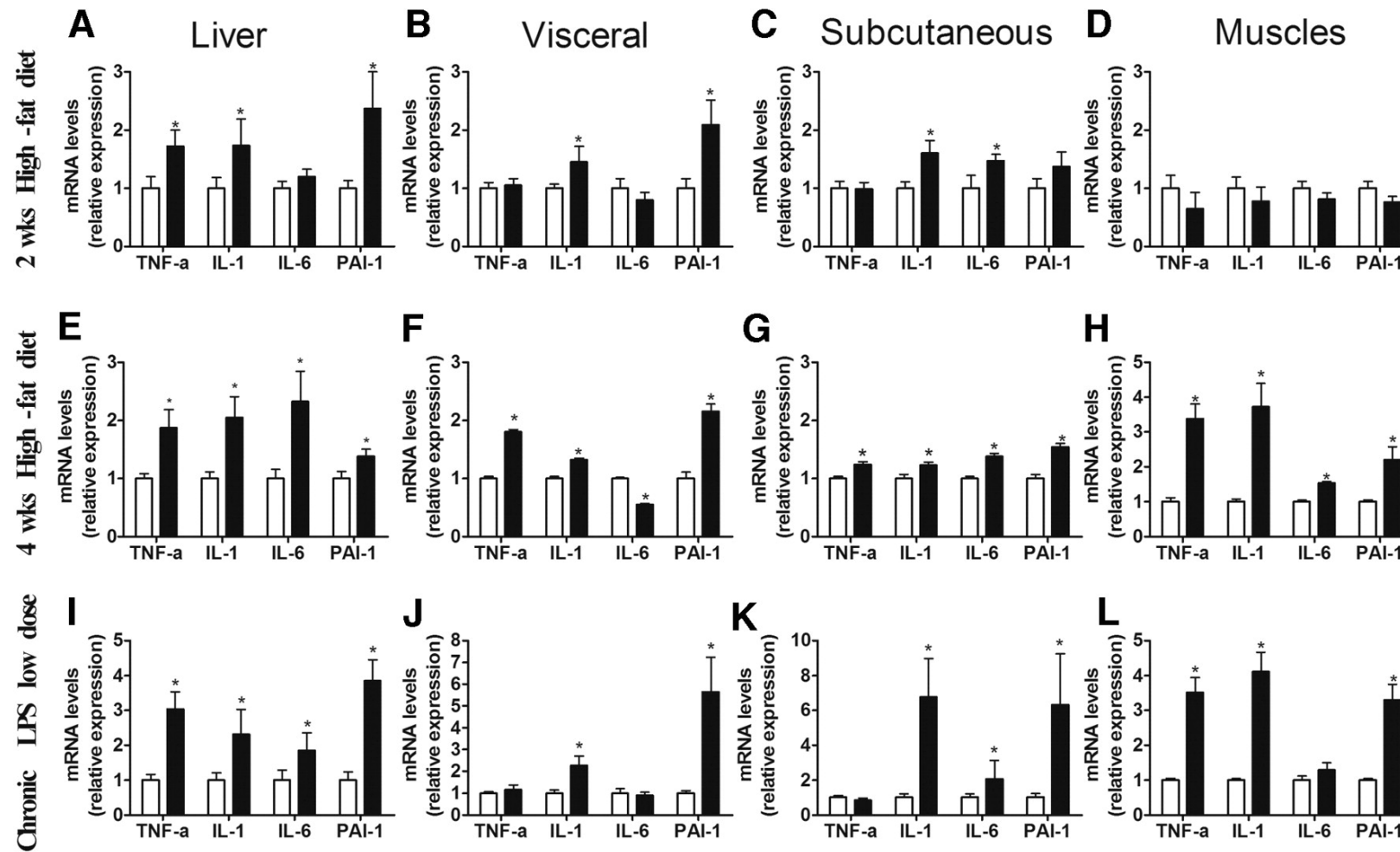
I was here first!

Chronic experimental metabolic endotoxemia induces obesity and diabetes.



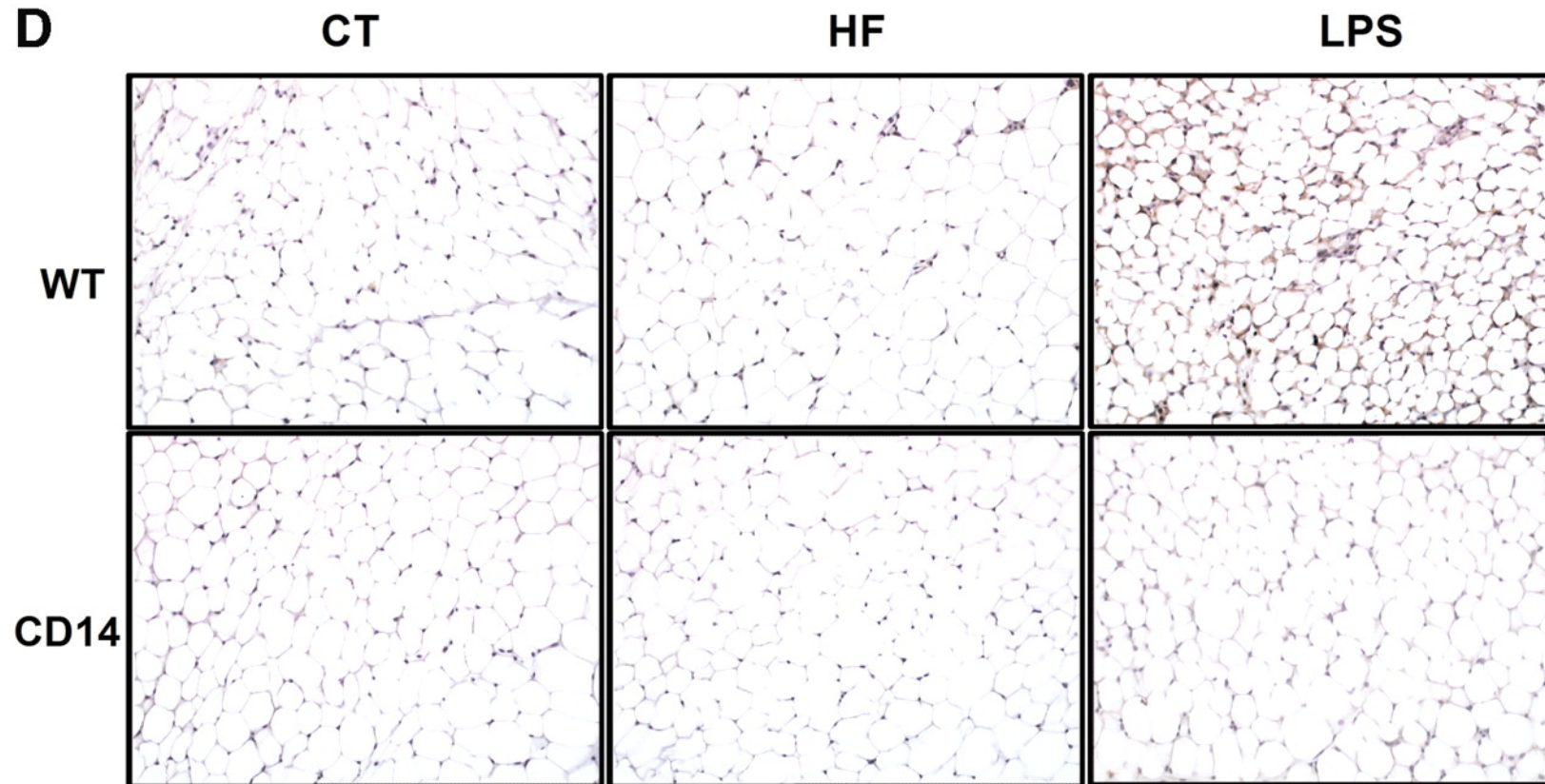
Patrice D. Cani et al. Diabetes 2007;56:1761-1772

Metabolic endotoxemia triggers the expression of inflammatory factors similarly to high-fat feeding.



Patrice D. Cani et al. Diabetes 2007;56:1761-1772

Metabolic endotoxemia impairs adipocyte morphology.



Patrice D. Cani et al. *Diabetes* 2007;56:1761-1772

[Diabetes Care](#). 2012 Feb;35(2):375-82. doi: 10.2337/dc11-1593. Epub 2011 Dec 30.

High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects.

[Harte AL](#)¹, [Varma MC](#), [Tripathi G](#), [McGee KC](#), [Al-Daghri NM](#), [Al-Attas OS](#), [Sabico S](#), [O'Hare JP](#), [Ceriello A](#), [Saravanan P](#), [Kumar S](#), [McTernan PG](#).

“It is known that low-grade chronic systemic inflammation contributes to this risk, which appears altered by several factors such as increasing age, sex, ethnicity, genetics, and dietary influences. However, systemic inflammation appears to persist in type 2 diabetic subjects, despite medication, while the mechanisms and mediators of this continual inflammation appear less clear.”

*“...clinical studies have also implicated gut-derived endotoxin as a “**primary insult**” to activate the inflammatory state, contributing to metabolic disease, with current cross-sectional data showing elevated systemic endotoxin levels in conditions of obesity, type 2 diabetes, coronary artery disease, and fatty liver disease ([8](#),[10](#),[11](#),[14–17](#)). Within these studies, circulating endotoxin is observed to be positively associated with waist circumference, waist-to-hip ratio, insulin levels, inflammatory cytokines and lipids, including total cholesterol, triglycerides (TGs), and LDL cholesterol, and negatively associated with HDL cholesterol ([8](#),[10](#),[11](#),[14–17](#)).”*



Article

LPS-Induced Low-Grade Inflammation Increases Hypothalamic JNK Expression and Causes Central Insulin Resistance Irrespective of Body Weight Changes

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† These authors contribute equally to this study.

Received: 26 April 2017; Accepted: 27 June 2017; Published: 4 July 2017

Abstract: Metabolic endotoxemia contributes to low-grade inflammation in obesity, which causes insulin resistance due to the activation of intracellular proinflammatory pathways, such as the c-Jun N-terminal Kinase (JNK) cascade in the hypothalamus and other tissues. However, it remains unclear whether the proinflammatory process precedes insulin resistance or it appears because of the development of obesity. Hypothalamic low-grade inflammation was induced by prolonged lipopolysaccharide (LPS) exposure to investigate if central insulin resistance is induced by

“The present data suggest that an increased JNK activity in the hypothalamus underlies the development of insulin resistance during prolonged exposure to endotoxins. Our study reveals that weight gain is not mandatory for the development of hypothalamic insulin resistance and the blockade of proinflammatory pathways could be useful for restoring the insulin signaling during prolonged low-grade inflammation as seen in obesity.”

“The gut microbiota has recently been recognized as a key environmental factor driving metabolic diseases. In fact, the gut microbiota is even seen as a separate endocrine organ, which is involved, through a molecular crosstalk with the host, in the maintenance of host energy homeostasis and in the stimulation of host immunity.”

“...a healthy or dysbiotic gut microbiota affects the gut and metabolic health of the host through modulation of gut physiology and LPS infiltration, calorie intake, fat accumulation, and insulin action.”

Boulangé et al. *Genome Medicine* (2016) 8:42
DOI 10.1186/s13073-016-0303-2

Genome Medicine

REVIEW

Open Access



Impact of the gut microbiota on inflammation, obesity, and metabolic disease

Claire L. Boulangé¹, Ana Luisa Neves², Julien Chilloux², Jeremy K. Nicholson^{1,2*} and Marc-Emmanuel Dumas^{2*}

Abstract

The human gut harbors more than 100 trillion microbial cells, which have an essential role in human metabolic regulation via their symbiotic interactions with the host. Altered gut microbial ecosystems have been associated with increased metabolic and immune disorders in animals and humans. Molecular interactions linking the gut microbiota with host energy metabolism, lipid accumulation, and immunity have also been identified. However, the exact mechanisms that link specific variations in the composition of the gut microbiota with the development of obesity and metabolic diseases in humans remain obscure owing to the complex etiology of these pathologies. In this review, we discuss current knowledge about the mechanistic interactions between the gut microbiota, host energy metabolism, and the host immune system in the context of obesity and metabolic disease, with a focus on the importance of the axis that links gut microbes and host metabolic inflammation. Finally, we discuss therapeutic approaches aimed at reshaping the gut microbial ecosystem to regulate obesity and related pathologies, as well as the challenges that remain in this area.

Metabolic endotoxemia: a molecular link between obesity and cardiovascular risk

Ana Luísa Neves¹, João Coelho¹, Luciana Couto², Adelino Leite-Moreira¹
and Roberto Roncon-Albuquerque Jr¹

Departments of ¹Physiology and Cardiothoracic Surgery ²General Practice, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro; 4200-319 Porto, Portugal

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Abstract

Obesity is associated with significantly increased cardiovascular (CV) risk and mortality. Several molecular mechanisms underlying this association have been implied, among which the intestinal barrier has gained a growing interest. In experimental models of obesity, significant alterations in the intestinal barrier lead to increased intestinal permeability.

Key Words

- endotoxemia
- obesity
- cardiovascular diseases



ENGIHR SUPPLEMENT

Dysbiosis of the gut microbiota in disease

**Simon Carding^{1,2}, Kristin Verbeke³, Daniel T. Vipond^{1,2}, Bernard M. Corfe^{4,5*}
and Lauren J. Owen⁶**

¹Institute of Food Research, Norwich, UK; ²Norwich Medical School, University of East Anglia, Norwich, UK;

³Translational Research in Gastrointestinal Disorders, KU Leuven, Leuven, Belgium; ⁴Molecular Gastroenterology Research Group, Department of Oncology, University of Sheffield, Sheffield, UK; ⁵Insigneo Institute for in silico Medicine, University of Sheffield, Sheffield, UK; ⁶Human Nutrition Unit, Department of Oncology, University of Sheffield, Sheffield, UK

There is growing evidence that dysbiosis of the gut microbiota is associated with the pathogenesis of both intestinal and extra-intestinal disorders. Intestinal disorders include inflammatory bowel disease, irritable bowel syndrome (IBS), and coeliac disease, while extra-intestinal disorders include allergy, asthma, metabolic syndrome, cardiovascular disease, and obesity.

In many of these conditions, the mechanisms leading to disease development involves the pivotal mutualistic relationship between the colonic microbiota, their metabolic products, and the host immune system. The establishment of a 'healthy' relationship early in life appears to be critical to maintaining intestinal homeostasis.

METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

Metabolic Endotoxemia Initiates Obesity and Insulin Resistance

Patrice D. Cani, Jacques Amar, et al.

Diabetes 2007 Jul; 56(7): 1761-1772. <https://doi.org/10.2337/db06-1491>

Metabolic endotoxemia directly increases the proliferation of adipocyte precursors at the onset of metabolic diseases through a CD14-dependent mechanism

Elodie Luche, Béatrice Cousin, et al.

Mol Metab. 2013 Aug; 2(3): 281–291.

Lipopolysaccharide Causes an Increase in Intestinal Tight Junction Permeability in Vitro and in Vivo by Inducing Enterocyte Membrane Expression and Localization of TLR-4 and CD14

Shuhong Guo, Rana Al-Sadi, Hamid M. Said, and Thomas Y. Ma

The American Journal of Pathology, Vol. 182, No. 2, February 2013

Elevated endotoxin levels in non-alcoholic fatty liver disease

Alison L Harte et al.

Journal of Inflammation 2010;7:15

Received: 3 September 2009 Accepted: 30 March 2010 Published: 30 March 2010



METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

[Cell Immunol.](#) 1991 Aug;136(1):219-33.

LPS promotes CB3-induced myocarditis in resistant B10.A mice.

[Lane JR](#)¹, [Neumann DA](#), [Lafond-Walker A](#), [Herskowitz A](#), [Rose NR](#).

[J Exp Med.](#) 1977 May 1;145(5):1250-63.

Induction of autoimmunity in good and poor responder mice with mouse thyroglobulin and lipopolysaccharide.

[Esquivel PS](#), [Rose NR](#), [Kong YC](#).

[Cell Immunol.](#) 2001 Oct 10;213(1):52-61.

Immunomodulation of murine cytomegalovirus-induced myocarditis in mice treated with lipopolysaccharide and tumor necrosis factor.

[Lenzo JC](#)¹, [Fairweather D](#), [Shellam GR](#), [Lawson CM](#).

[J Immunol.](#) 2005 Jul 15;175(2):959-66.

Lipopolysaccharide injection induces relapses of experimental autoimmune encephalomyelitis in nontransgenic mice via bystander activation of autoreactive CD4+ cells.

[Nogai A](#)¹, [Siffrin V](#), [Bonhagen K](#), [Pfueller CF](#), [Hohnstein T](#), [Volkmer-Engert R](#), [Brück W](#), [Stadelmann C](#), [Kamradt T](#).



CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions
Anorexia	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

Basic Clin Androl. 2016; 26: 7.

Published online 2016 Jun 22. doi: 10.1186/s12610-016-0034-7

PMCID: PMC4918028

Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING) - a novel theory for the development of late onset hypogonadism in obese men.

Kelton Tremellen

- **Male obesity is associated with late onset hypogonadism, a condition characterized by decreased serum testosterone, sperm quality plus diminished fertility and quality of life.**
- **The GELDING theory (Gut Endotoxin Leading to a Decline IN Gonadal function) – describes the development of obesity related hypogonadism.**

“Several observational studies have previously reported an association between obesity related hypogonadism (low testosterone) and systemic inflammation. However, for the first time we postulate that the trans-mucosal passage of bacterial lipopolysaccharide (LPS) from the gut lumen into the circulation is a key inflammatory trigger underlying male hypogonadism.”

“Endotoxin is known to reduce testosterone production by the testis, thereby also leading to a decline in sperm production.”

“Testosterone is known to be a powerful immune-suppressive, decreasing a man’s ability to fight infection. Therefore we postulate that the male reproductive axis has evolved the capacity to lower testosterone production during times of infection and resulting endotoxin exposure, decreasing the immunosuppressive influence of testosterone, in turn enhancing the ability to fight infection. While this response is adaptive in times of sepsis, it becomes maladaptive in the setting of “non-infectious” obesity related metabolic endotoxemia.”

GUT PERMEABILITY – CHRONIC INFLAMMATION

Stress induces endotoxemia and increasing barrier permeability

Karin de Punder* and Leo Pruimboom

Frontiers in Immunology published: 15 May 2015

“Chronic non-communicable diseases (NCDs) are the leading causes of work absence, disability, and mortality worldwide. Most of these diseases are associated with low-grade inflammation.”

“In combination with modern life-style factors, the increase in **bacteria/bacterial toxin translocation** arising from a more **permeable intestinal** wall causes a low-grade inflammatory state. We support this hypothesis with numerous studies finding **associations with NCDs and markers of endotoxemia**, suggesting that this process plays a pivotal and perhaps even **a causal role** in the development of low-grade inflammation and its related diseases.”

GROUND ZERO OF MOST HEALTH

HOW DOES A HEALTHY MICROBIOME PROTECT AGAINST METABOLIC ENDOTOXEMIA?

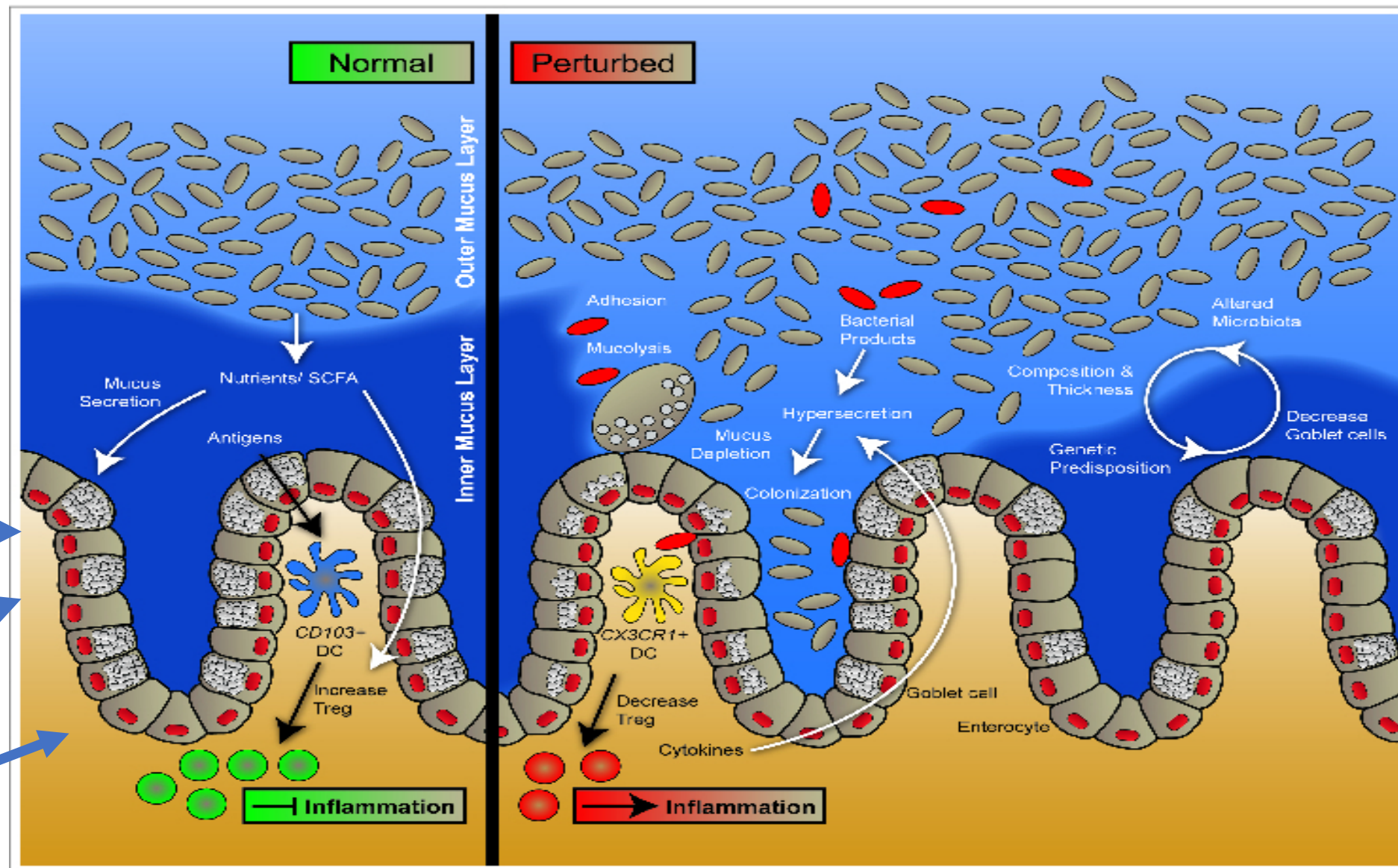
Neutralize LPS
-increase sIgA
-increase PAMP
-manages microbiome

Increase Mucin2
production

Increase tight
junction protein
expression

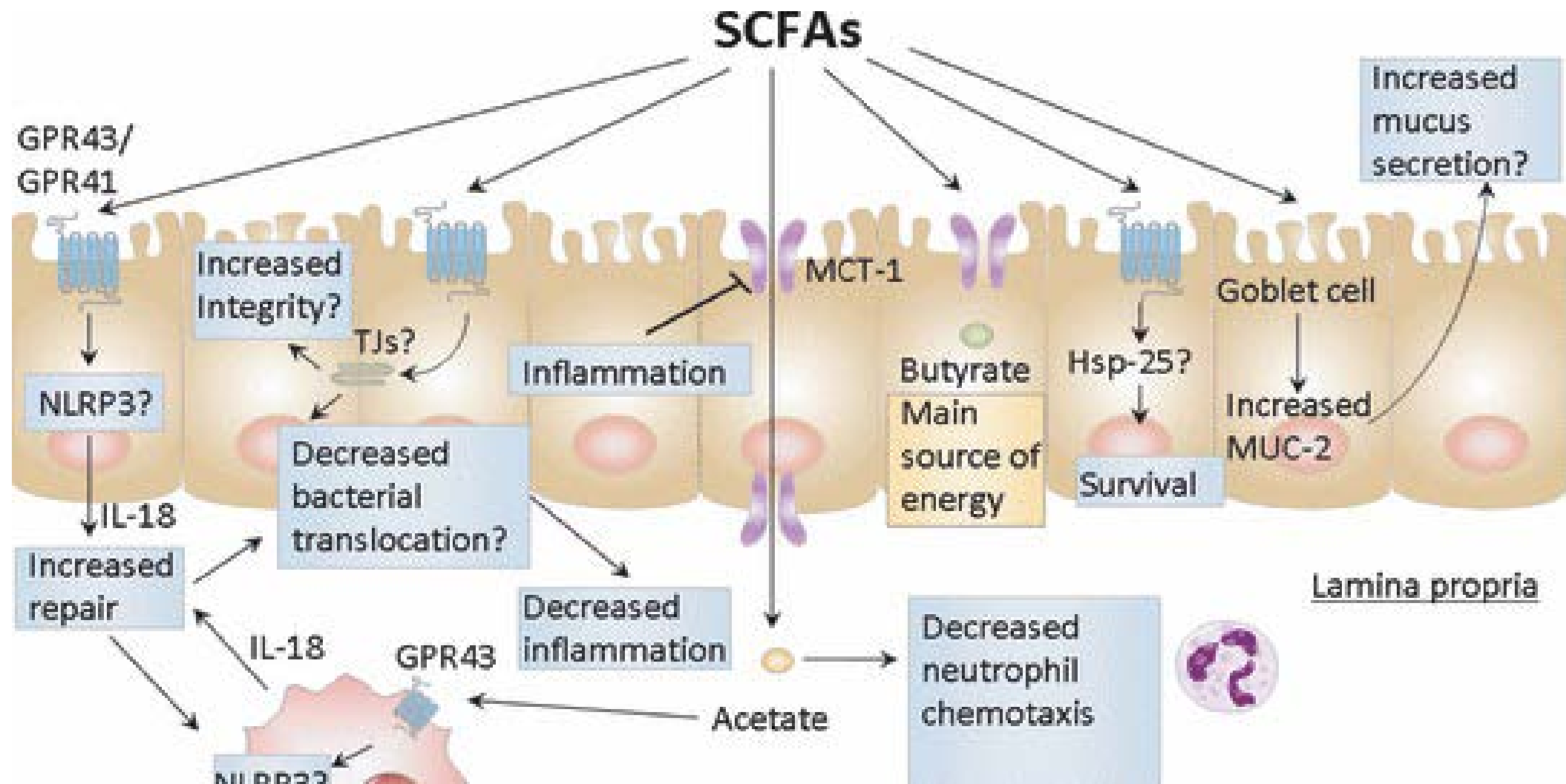
Increase
regeneration of
expelled IEC

Reduce inflammatory
response with
metabolites, indole-3-
propionate, intectin



[Tissue Barriers. 2015; 3\(1-2\): e982426.](#) Published online 2015 Jan 15. doi: [10.4161/21688370.2014.982426](#)

SHORT CHAIN FATTY ACIDS



[Benef Microbes](#). 2016;7(2):181-94. doi: 10.3920/bm2015.0062. Epub 2015 Dec 8.

Gut microbiota in health and disease: an overview focused on metabolic inflammation.

[Nagpal R](#)¹, [Kumar M](#)², [Yadav AK](#)², [Hemalatha R](#)², [Yadav H](#)³, [Marotta F](#)⁴, [Yamashiro Y](#)¹.

Author information

Abstract

In concern to the continuously rising global prevalence of obesity, diabetes and associated diseases, novel preventive and therapeutic approaches are urgently required. However, to explore and develop such innovative strategies, a meticulous comprehension of the biological basis of these diseases is extremely important. Past decade has witnessed an enormous amount of research investigation and advancement in the field of obesity, diabetes and metabolic syndrome, with the gut microbiota receiving a special focus in the triangle of nutrition, health and diseases. In particular, the role of gut microbiota in health and diseases has been one of the most vigorous and intriguing field of recent research; however, much still remains to be elucidated about its precise role in host metabolism and immune functions and its implication in the onset, progression as well as in the amelioration of metabolic ailments. **Recent investigations have suggested a significant contribution of the gut microbiota in the regulation and impairment of energy homeostasis, thereby causing metabolic disorders, such as metabolic endotoxemia, insulin resistance and type 2 diabetes.** Numerous inflammatory biomarkers have been found to be associated with obesity, diabetes and risk of other associated adverse outcomes, thereby suggesting that a persistent low-grade inflammatory response is a potential risk factor. In this milieu, this review intends to discuss potential evidences supporting the disturbance of the gut microbiota balance and the intestinal barrier permeability as a potential triggering factor for systemic inflammation in the onset and progression of obesity, type 2 diabetes and metabolic syndrome.

[Am J Physiol Gastrointest Liver Physiol.](#) 2017 Jun 1;312(6):G559-G571. doi: 10.1152/ajpgi.00066.2017. Epub 2017 Mar 23.

Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress.

[Karl JP](#)¹, [Margolis LM](#)², [Madslien EH](#)³, [Murphy NE](#)², [Castellani JW](#)⁴, [Gundersen Y](#)³, [Hoke AV](#)^{5,6}, [Levangie MW](#)^{5,6}, [Kumar R](#)⁷, [Chakraborty N](#)^{5,6}, [Gautam A](#)⁵, [Hammamieh R](#)⁵, [Martini S](#)³, [Montain SJ](#)², [Pasiakos SM](#)².

Author information

Abstract

The magnitude, temporal dynamics, and physiological effects of intestinal microbiome responses to physiological stress are poorly characterized. This study used a systems biology approach and a multiple-stressor military training environment to determine the effects of physiological stress on intestinal microbiota composition and metabolic activity, as well as intestinal permeability (IP). Soldiers ($n = 73$) were provided three rations per day with or without protein- or carbohydrate-based supplements during a 4-day cross-country ski-march (STRESS). IP was measured before and during STRESS. Blood and stool samples were collected before and after STRESS to measure inflammation, stool microbiota, and stool and plasma global metabolite profiles. IP increased $62 \pm 57\%$ (mean \pm SD, $P < 0.001$) during STRESS independent of diet group and was associated with increased inflammation. Intestinal microbiota responses were characterized by increased α -diversity and changes in the relative abundance of $>50\%$ of identified genera, including increased abundance of less dominant taxa at the expense of more dominant taxa such as *Bacteroides*. Changes in intestinal microbiota composition were linked to 23% of metabolites that were significantly altered in stool after STRESS. Together, pre-STRESS Actinobacteria relative abundance and changes in serum IL-6 and stool cysteine concentrations accounted for 84% of the variability in the change in IP. Findings demonstrate that a multiple-stressor military training environment induced increases in IP that were associated with alterations in markers of inflammation and with intestinal microbiota composition and metabolism. Associations between IP, the pre-STRESS microbiota, and microbiota metabolites suggest that targeting the intestinal microbiota could provide novel strategies for preserving IP during physiological stress.

NEW & NOTEWORTHY Military training, a unique model for studying temporal dynamics of intestinal barrier and intestinal microbiota responses to stress, resulted in increased intestinal permeability concomitant with changes in intestinal microbiota composition and metabolism. Prestress intestinal microbiota composition and changes in fecal concentrations of metabolites linked to the microbiota were associated with increased intestinal permeability. Findings suggest that targeting the intestinal microbiota could provide novel strategies for mitigating increases in intestinal permeability during stress.



PROBIOTICS

??!!

THE SPORE SOLUTION

[J Interferon Cytokine Res.](#) 2016 Feb;36(2):Effects of Bacillus subtilis on Epithelial Tight Junctions of Mice with Inflammatory Bowel Disease.

[Gong Y](#)¹, [Li H](#)¹, [Li Y](#)¹.

“B. subtilis intake upregulated expression of TJ proteins(claudin-1, occludin, JAM-A, and ZO-1), for improved barrier function, and downregulated cytokine expression (IL-6, IL-17, IL-23, and TNF- α) to reduce intestinal epithelial damage.”

[Comp Biochem Physiol A Mol Integr Physiol.](#) 2002 Sep;133(1):95-104.

Histological alterations of intestinal villi in chickens fed dried Bacillus subtilis var. natto.

[Samanya M](#)¹, [Yamauchi KE](#).

“These birds had a tendency to display greater growth performance and intestinal histologies, such as villus height, cell area and cell mitosis, than the controls. ”

***Bacillus subtilis* Protects Porcine Intestinal Barrier from Deoxynivalenol via Improved Zonula Occludens-1 Expression**

[Min Jeong Gwa, Sun Kwang Songa, Sung Moo Park](#)

“B. subtilis may have potential to enhance epithelial barrier function and to prevent the cells from DON-induced barrier dysfunction.”

Prospective Study

Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers

Brian K McFarlin, Andrea L Henning, Erin M Bowman, Melody M Gary, Kimberly M Carbajal

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Author contributions: McFarlin BK designed the study, collected data, interrupted findings, and prepared manuscript; Henning AL, Bowman EM, Gary MM and Carbajal KM collected data, interrupted findings, and prepared manuscript.

Institutional review board statement: The study was reviewed

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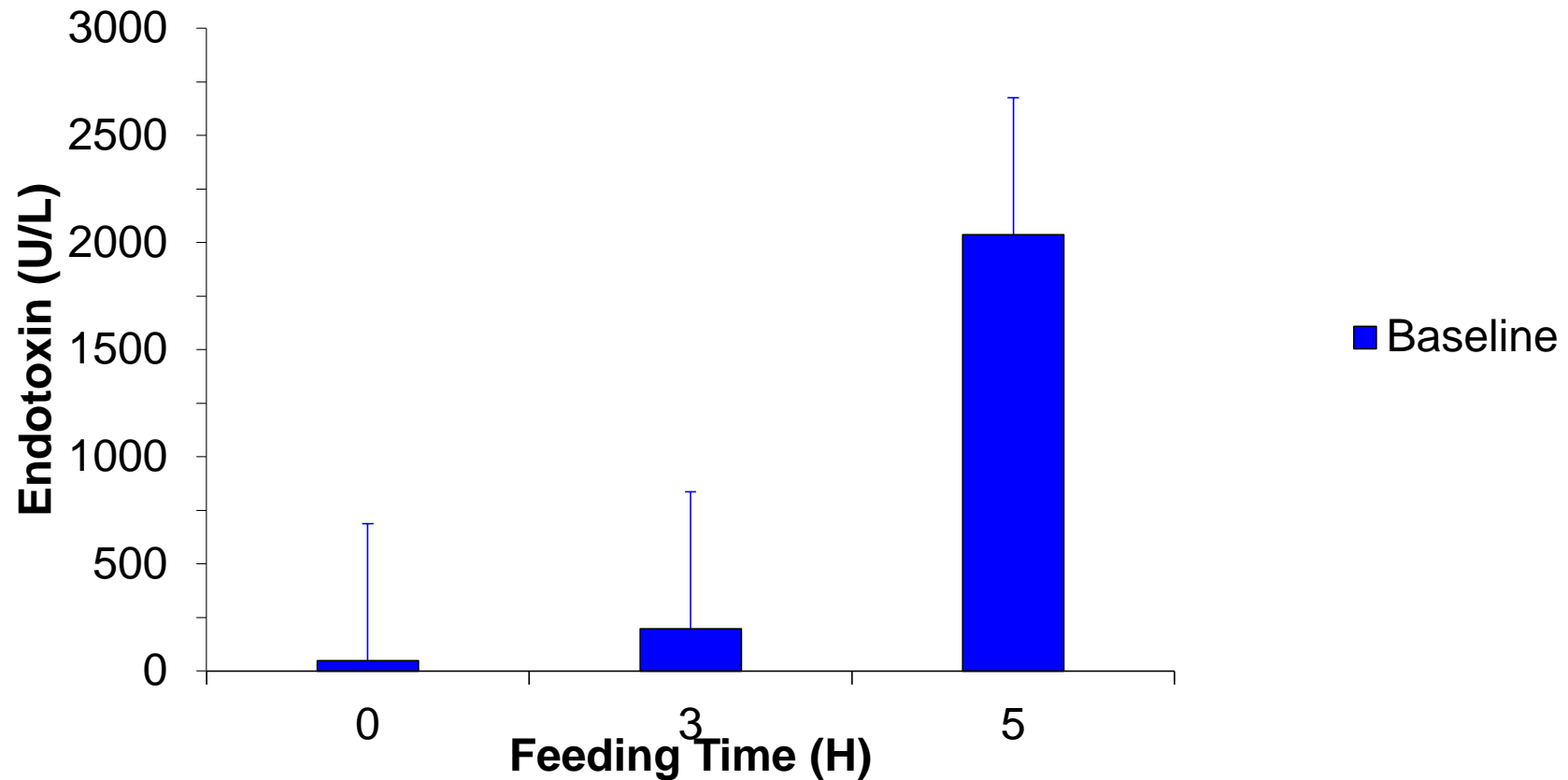
Manuscript source: Invited manuscript

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Received: January 26, 2017
Peer-review started: February 8, 2017
First decision: April 17, 2017

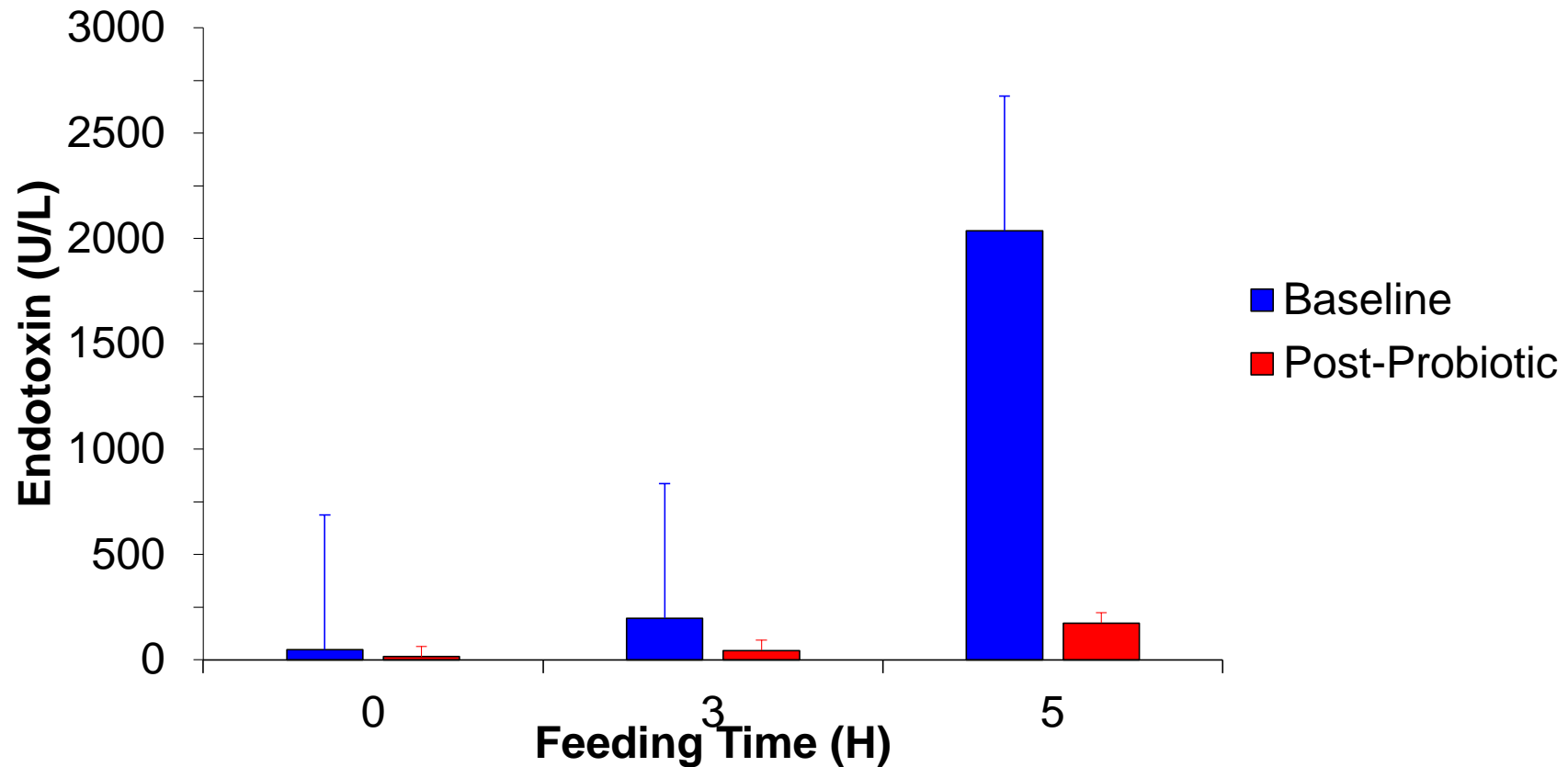
The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: Pilot Study

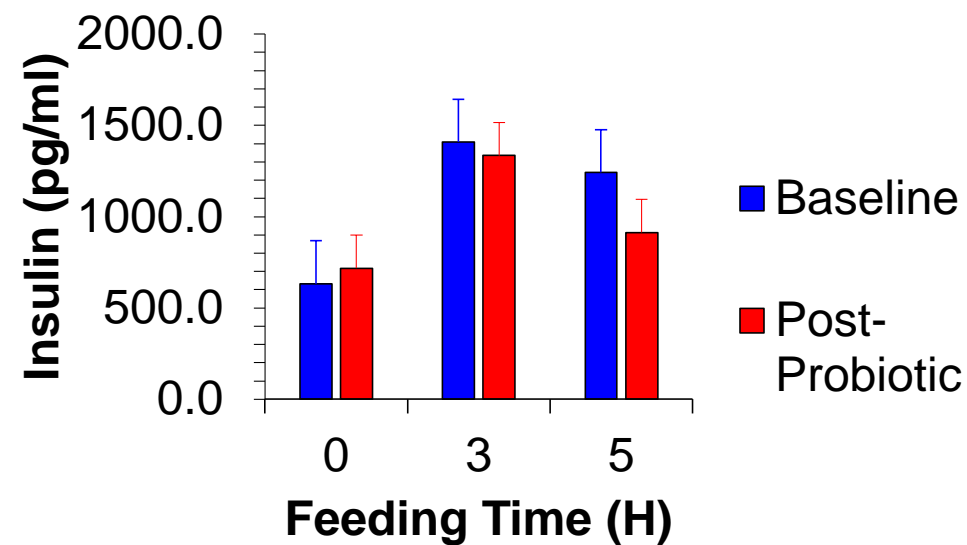
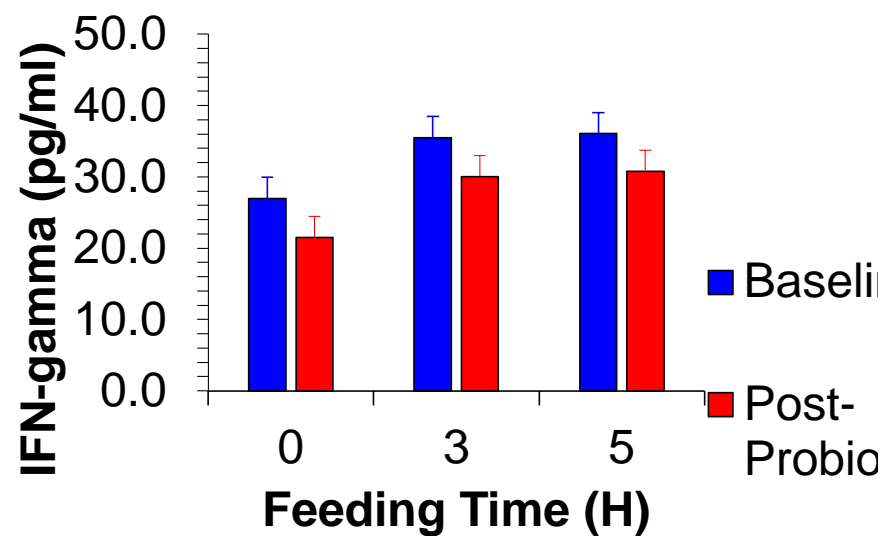
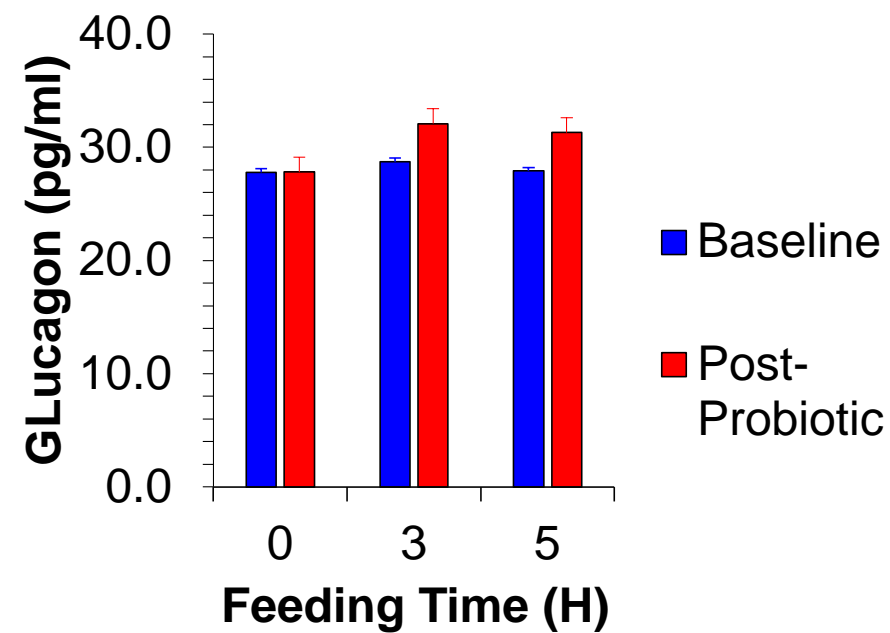
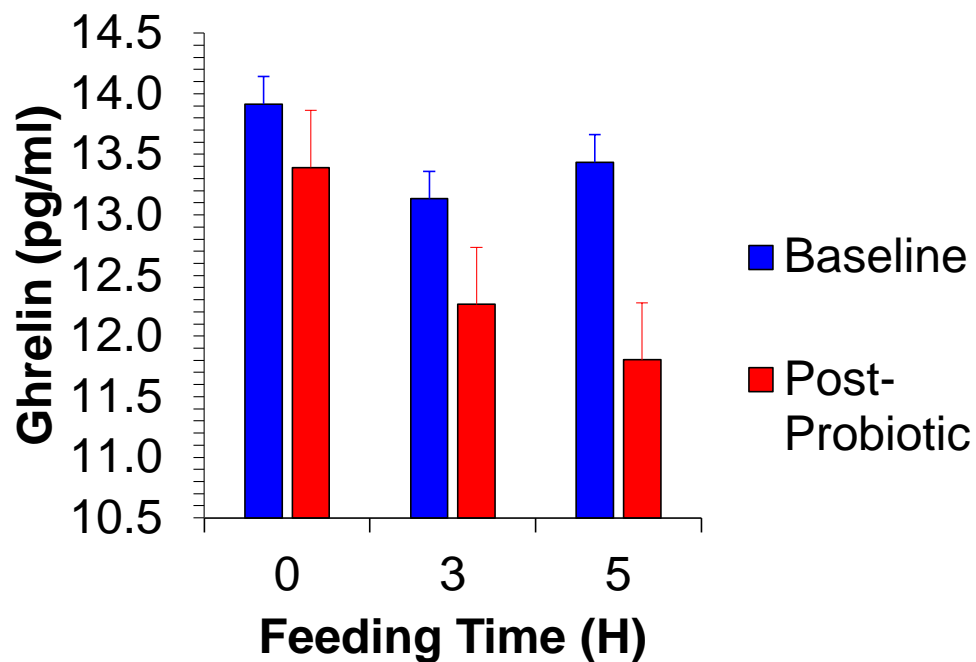
Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



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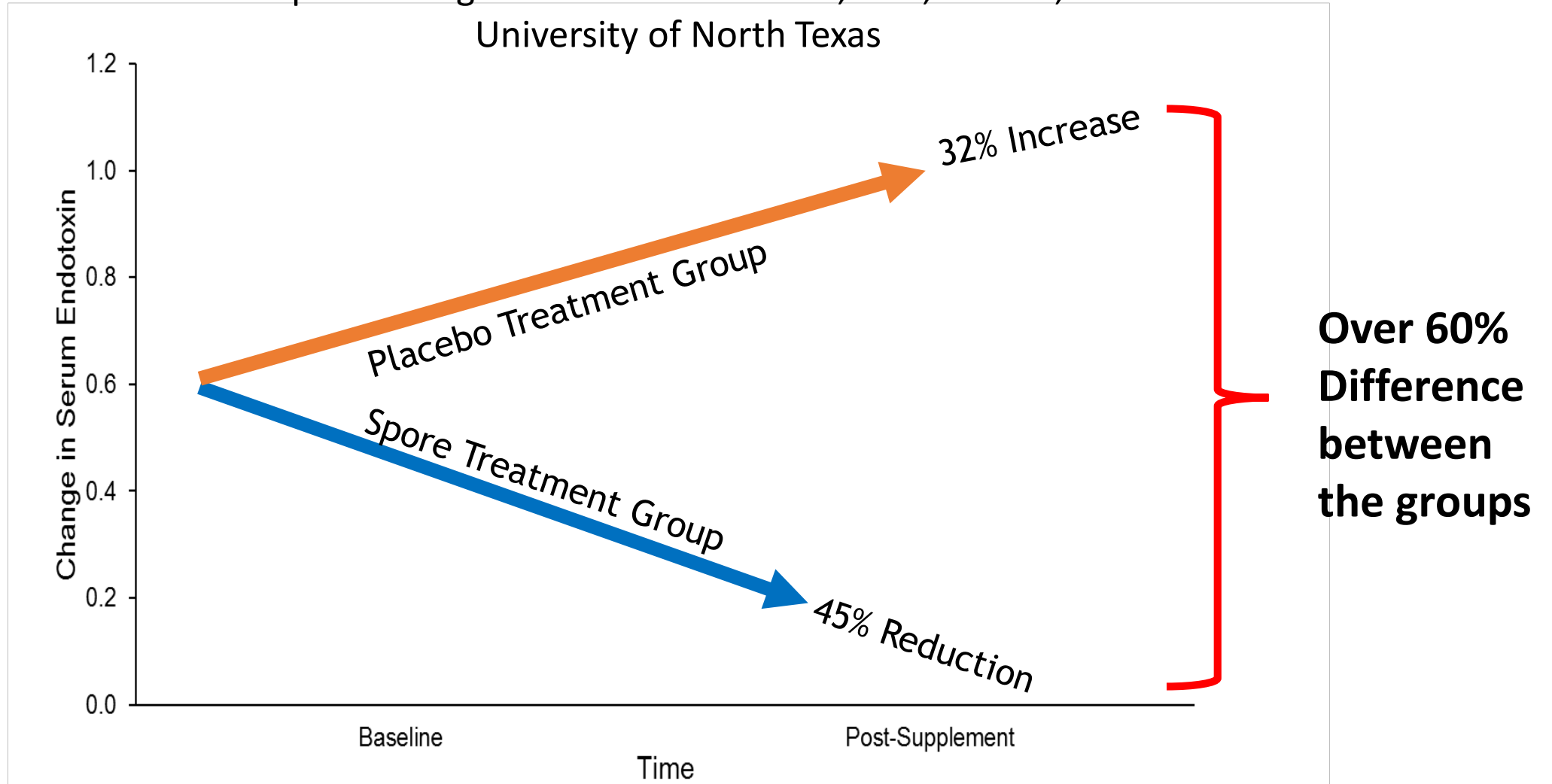
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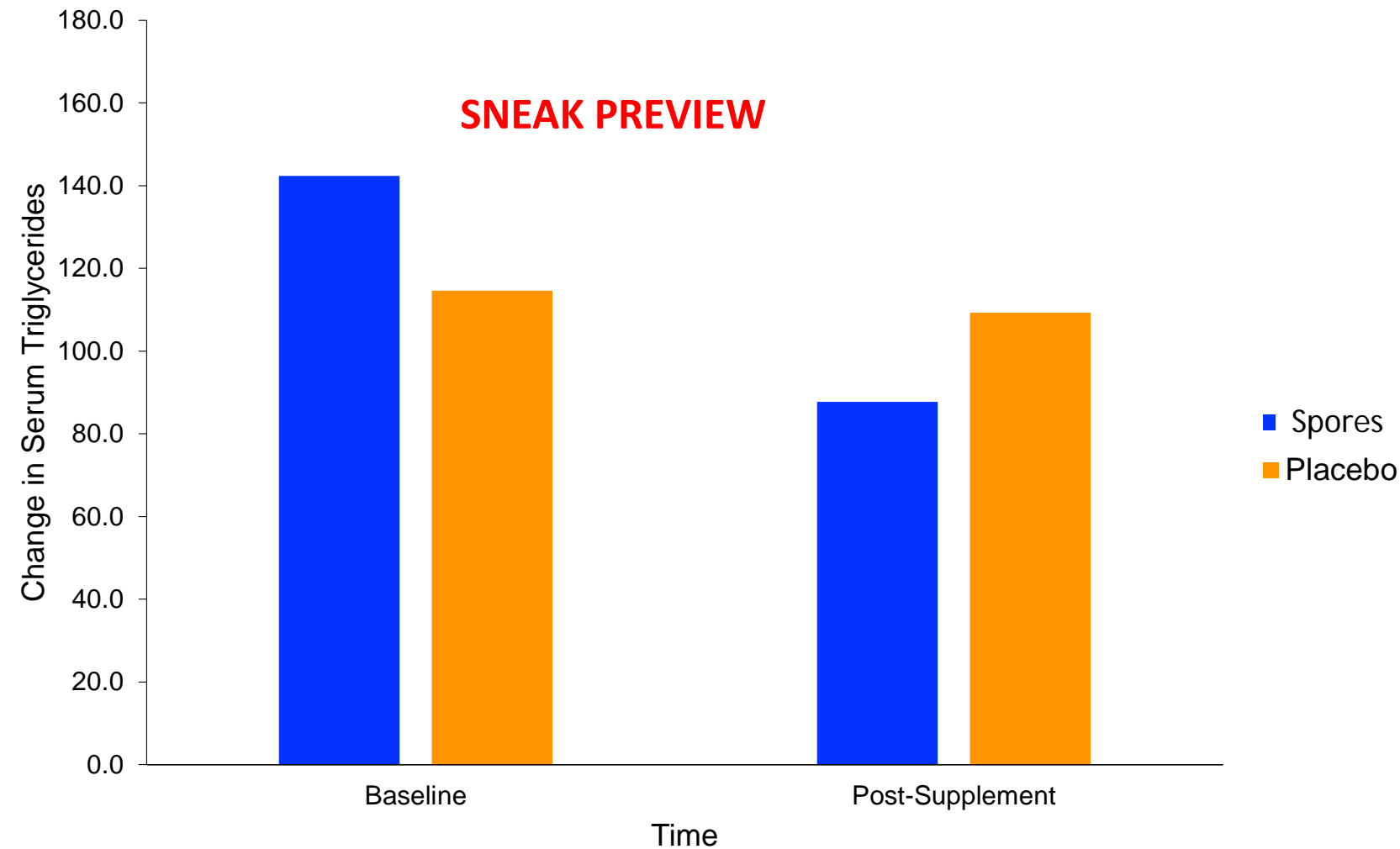
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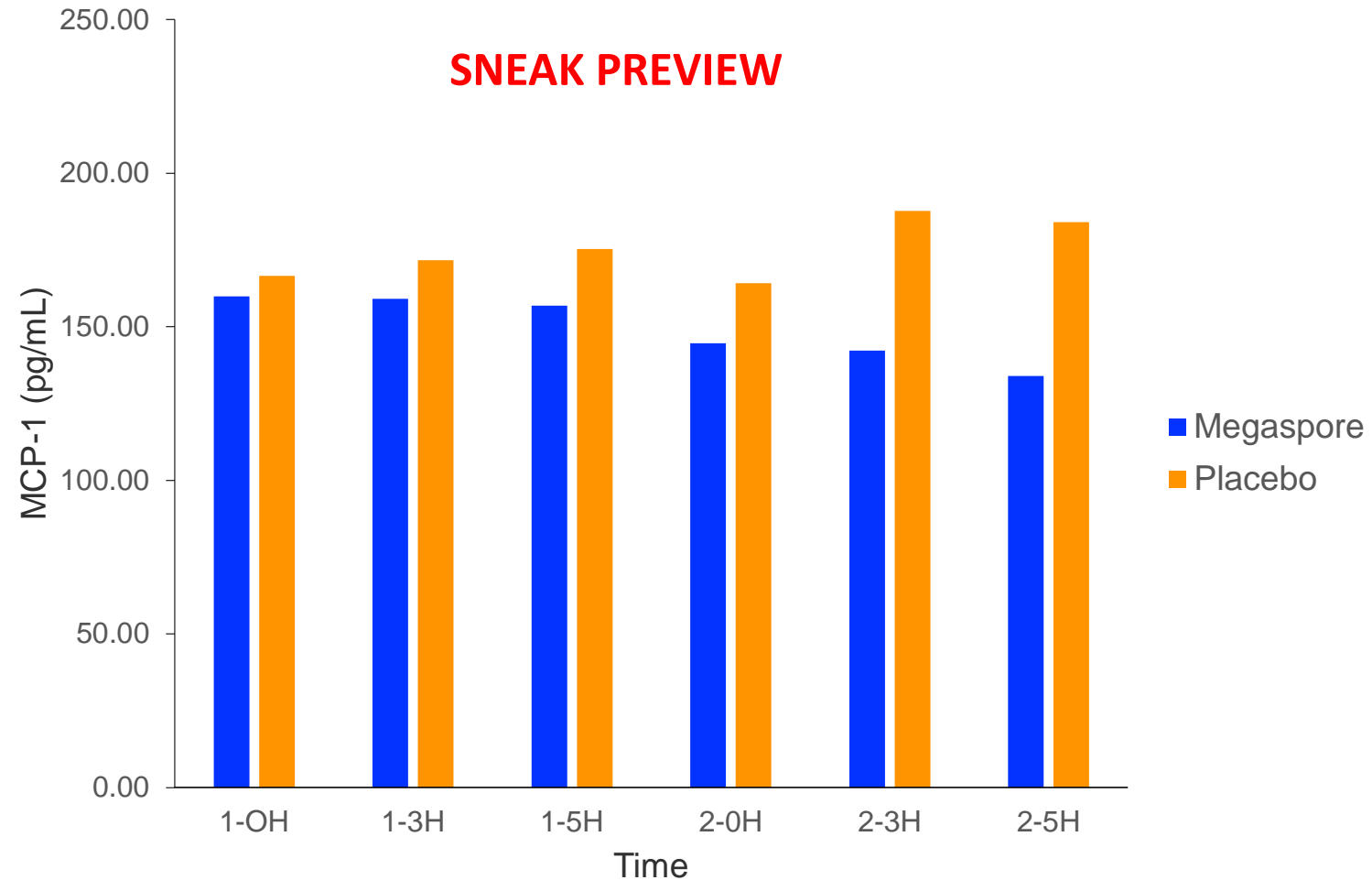
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Variables Significantly Effected
by Probiotic

Variables Not Significantly Effected by
Probiotic

Variable	30-d Supplementation					
	Spore-based Probiotic			Placebo		
	Pre	3-h	5-h	Pre	3-h	5-h
Endotoxin						
Triglycerides						
Ghrelin						
MCP-1						
IL-12p70						
IL-1beta						
IL-6						
IL-8						
Glucose						
Insulin						
Leptin						
GM-CSF						
IL-4						
IL-5						
IL-7						
IL-10						
IL-13						
TNF-alpha						

WHAT CAN WE DO??

INCREASE DIVERSITY

- Time restricted feeding
- Methodical fiber increase
- Macronutrient Diversity

CHANGE EXPOSURE

- Get Dirty!
- Eliminate chlorine cleaners
- Eliminate antimicrobial products
- Get a dog
- Protect from EMFs

INCREASE sIgA

- Supplements that help: essential fatty acids, glutathione, glycine, glutamine, phosphatidylcholine, Vitamin C and Zinc
- Probiotics: *Lactobacillus* spores and *saccharomyces* – possibly *Lactococcus*
- Address the adrenals
- Stress reduction

BUTYRATE and SCFA!

IMPROVE BUTYRATE PRODUCTION

- Key nutrients are: L-threonine, L-serine, L-proline and L-cysteine. 95% increase in mucin2 production in male rats treated with DSS (dextran sulfate sodium)
- Increase butyrate
- Increase autophagosomes by autophagy

RESOLVE LEAKY GUT

- Spore based probiotic
- L-glutamine
- Reduce saturated and oxidized fats
- Lactoferrin

Thank You

Questions or more information?

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