The Role of the Microbiome in Brain Health and Disease

David Perlmutter, MD, FACN, ABIHM

Faculty Disclosure

David Perlmutter, MD, FACN, ABIHM

Relationships with commercial interests:

Paid Consultant - Garden of Life
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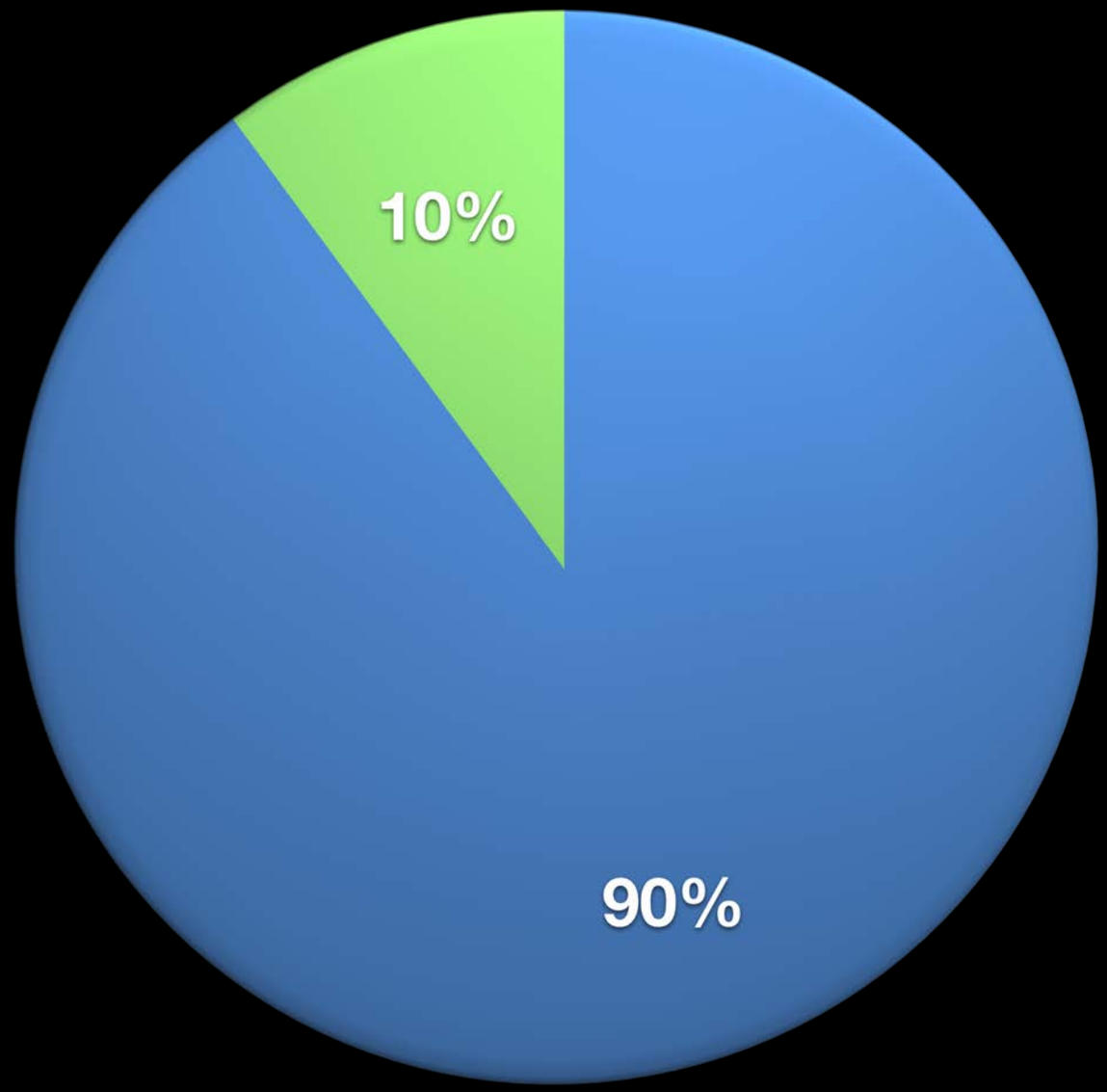
Presentation Learning Objectives

After participating in this presentation, clinicians should be better able to:

- Understand the pivotal role of the microbiome in determining brain health and functionality
- Recognize the detrimental effects of common medications in terms of threatening microbial diversity
- Expand their tool boxes in terms of dealing with common degenerative conditions

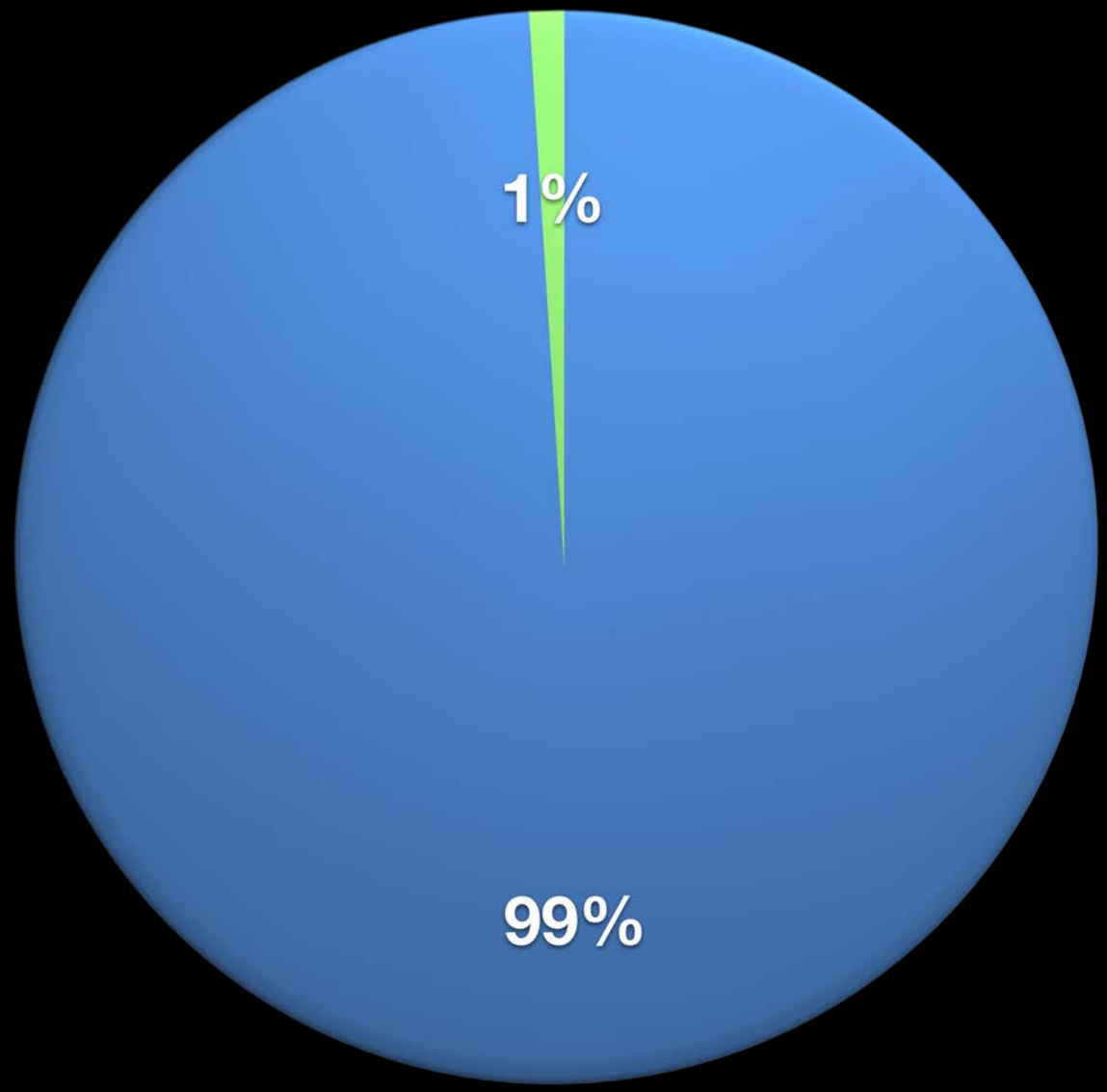
mammalian cells

microbial cells



mammalian DNA

microbial DNA



Inflammation

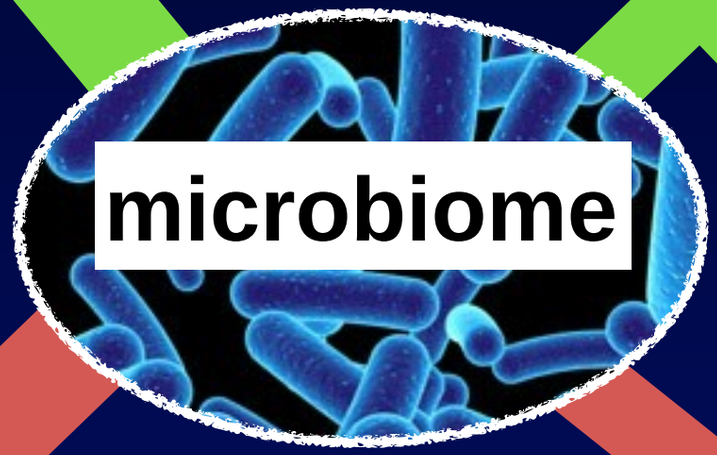
- Alzheimer’s disease
- Parkinson’s disease
- Autism
- Multiple sclerosis
- Stroke
- Depression
- ADHD

Commensal flora and the regulation of inflammatory and autoimmune responses

Seminars in Immunology 23 (2011) 139–145

Factors for Symbiosis
high fiber diet
natural birth
breast feeding
exposure to microbes
consumption of probiotics
favorable genetics

Effects of Symbiosis
resolution of inflammation
epithelial barrier integrity
regulation of neutrophil activity
reduced T-helper 17 cells
increased Treg (supressor)



Factors for Dysbiosis
antibiotic use
antibiotics in livestock
obesity
Western diet
hygeine
stress
pathogenic bacteria

Effects of Dysbiosis
inflammation
cancer
autoimmunity

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[b], Monica Di Paola[c], Matteo Ramazzotti[a], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

[a]Department of Preclinical and Clinical Pharmacology, University of Florence, 50139 Firenze, Italy; [b]Department of Pediatrics, Meyer Children Hospital, University of Florence, 50133 Firenze, Italy; [c]Department of Biochemical Sciences, University of Florence, 50134 Firenze, Italy; [d]DNA Vision Agrifood S.A., B-6041 Gosselies, Belgium; and [e]Laboratorio Interdipartimentale di Spettrometria di Massa, University of Florence, 50139 Firenze, Italy

Edited* by Daniel L. Hartl, Harvard University, Cambridge, MA, and approved June 30, 2010 (received for review April 29, 2010)

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from inflammations and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.

metagenomics | nutrigenomics | biodiversity | 454-pyrosequencing | short-chain fatty acids

The human gut "metagenome" is a complex consortium of trillions of microbes, whose collective genomes contain at least 100 times as many genes as our own eukaryote genome (1). This essential "organ," the microbiome, provides the host with enhanced metabolic capabilities, protection against pathogens, education of the immune system, and modulation of gastrointestinal (GI) development (2).

We do not yet completely understand how the different environments and wide range of diets that modern humans around the world experience has affected the microbial ecology of the human gut.

Contemporary human beings are genetically adapted to the environment in which their ancestors survived and which conditioned their genetic makeup. In mammals, both diet and phylogeny influence the increase in bacterial diversity from carnivore to omnivore to herbivore (3). Dietary habits are considered one of the main factors contributing to the diversity of human gut microbiota (2). Profound changes in diet and lifestyle conditions began with the so-called "Neolithic revolution" with the introduction of agriculture and animal husbandry ≈10,000 y ago (4). After that time, food resources became more abundant and constant, the concentration of large populations in limited areas created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases (5). It has been hypothesized that bacteria specialized in human-associated niches, including our gut commensal flora, underwent intense transformation during the social and demographic changes that took place with the first Neolithic settlements (6).

Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, autoimmune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed (5), and it is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase (7). The GI microflora plays a crucial role in the pathogenesis of IBD (8), and recent studies demonstrate that obesity is associated with imbalance in the normal gut microbiota (9, 10).

The aim of this study was to compare the gut microbiota of children aged 1–6 y living in a village of rural Africa in an environment that still resembles that of Neolithic subsistence farmers with the gut microbiota of western European children of the same age, eating the diet and living in an environment typical of the developed world. These two childhood populations provided an attractive model for assessing the impact of many environmental variables on the gut microbiota.

In our study, we address three general questions regarding the geography and evolution of the human microbiota: (*i*) how is bacterial diversity partitioned within and between the two populations studied; (*ii*) is there a possible correlation between bacterial diversity and diet; and (*iii*) what is the distribution of well-known bacterial pathogens in the two populations, given the different hygienic and geographic conditions?

Results and Discussion

Characterization of Dietary Habits of Children from the Boulpon Rural Village and from Florence, Italy. In this study, we characterized the fecal microbiota of 14 healthy children from the Mossi ethnic

Author contributions: C.D.F., D.C., and P.L. designed research; C.D.F., M.D.P., S.M., and S.C. performed research; G.P. contributed new reagents/analytic tools; M.R. and J.B.P. analyzed data; and C.D.F., D.C., M.D.P., and P.L. wrote the paper.

The authors declare no conflict of interest.

*This Direct Submission article had a prearranged editor.

Freely available online through the PNAS open access option.

Data deposition: Data were submitted to the Sequence Read Archive (SRA) using SA tools (SAcreator and SAconverter, http://satlab.sourceforge.net/index.html). The dataset is available at http://www.ebi.ac.uk/ena/data/view/ERP000133.

[1]To whom correspondence should be addressed. E-mail: paolo.lionetti@unifi.it.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1005963107/-/DCSupplemental.

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Comparison of fecal microbiota:

- European children (EU)
- Rural African children Burkina Faso (BF)
- 16S rDNA sequencing and biochemical analysis

PNAS, June 30, 2010

Firmicutes **Bacteroidetes**

African

- Prevotella
- Xylanibacter

Bacteroidetes

- Acetitomaculum
- Faecalibacterium
- Subdoligranulum

Firmicutes

- Others

European

- Alistipes
- Bacteroides

Bacteroidetes

- Acetitomaculum
- Faecalibacterium
- Roseburia
- Subdoligranulum

Firmicutes

- Others

Germ Free

⬆ Fat

⬆ Fermicutes

⬇ Bacteriodites

Conventional

⬇ Fat

⬇ Fermicutes

⬆ Bacteriodites

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Increased gut microbial diversity and reduced quantities of potentially pathogenic strains in African flora would agree with the “old friend” hypothesis, indicating a role of microbiota in protecting children from pathogens as well as from gastrointestinal diseases.

PNAS, June 30, 2010

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Our results suggest that diet has a dominant role in shaping the gut microbiota. We can hypothesize that the reduction in richness we observe in EU compared with BF children, could indicate how the consumption of sugar, animal fat, and calorie-dense foods in industrialized countries is rapidly limiting the adaptive potential of the microbiota.

PNAS, June 30, 2010

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Ancient Human Microbiomes

Ancient human microbiomes

Christina Warinner [a], Camilla Speller [b], Matthew J. Collins [b], Cecil M. Lewis Jr. [a,*]

[a] Department of Anthropology, University of Oklahoma, 101 David L. Boren Blvd., Norman, OK 73019, USA
[b] Department of Archaeology, University of York, Wentworth Way, York, YO10 5DD, UK

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Feces
Dental calculus

ABSTRACT

Very recently, we discovered a vast new microbial self: the human microbiome. Our native microbiota interface with our biology and culture to influence our health, behavior, and quality of life, and yet we know very little about their origin, evolution, or ecology. With the advent of industrialization, globalization, and modern sanitation, it is intuitive that we have changed our relationship with microbes, but we have little information about the ancestral state of our microbiome, and we therefore lack a foundation for characterizing this change. High-throughput sequencing has opened up new opportunities in the field of paleomicrobiology, allowing us to investigate the evolution of the complex microbial ecologies that inhabit our bodies. By focusing on recent coprolite and dental calculus research, we explore how emerging research on ancient human microbiomes is changing the way we think about ancient disease and how archaeological studies can contribute to a medical understanding of health and nutrition today.

Introduction

Genetic sequencing has revolutionized our understanding of the tree of life and humans' place within it. The development of the Sanger method of DNA sequencing in 1977 and the polymerase chain reaction (PCR) method of DNA amplification in 1983 ushered in an explosion of genetic data that determined the phylogeny of humans and the great apes (Ruvolo, 1997), rejected the biological concept of race in humans (Long and Kittles, 2003), and reconstructed the peopling of the world (Oppenheimer, 2012). The arrival of next generation sequencing (NGS) in the late 1990s facilitated the sequencing of the first complete human genome (Venter et al., 2001), and the subsequent commercial release of this technology in the mid-2000s enabled the genome sequencing of archaic humans, including Neanderthals (Green et al., 2010; Prufer et al., 2014), Denisovans (Krause et al., 2010; Reich et al., 2010; Meyer et al., 2012), and the mitochondrial genome of an archaic hominin classified as *Homo heidelbergensis* (Meyer et al., 2014), resulting in discoveries that have further reorganized and refined the human family tree. These studies have addressed fundamentally important aspects of human evolution. Nevertheless, the human genome encompasses only a fraction of the total genetic diversity found within humans. The collective microbial communities inhabiting the human body, known as the human microbiome, contain a vast amount of genetic and functional diversity far exceeding that of our own nuclear and mitochondrial genomes (Qin et al., 2010). A growing appreciation of the role of microbiomes in host essential life functions, the etiology of disease, and even speciation (Human Microbiome Project Consortium, 2012; Blaser et al., 2013; Brucker and Bordenstein, 2013; McFall-Ngai et al., 2013) challenges conventional views of the biological species concept (Mayr, 1963; Brucker and Bordenstein, 2013) and raises the question of whether or not ancient human microbiomes should also be investigated in order to explore broader issues in human evolution. This paper will discuss the relationship between humans and their microbiomes and review new developments in the emerging field of ancient microbiome research. We argue that only by also exploring our microbiomes both today and in the past can we fully understand what it means to be human.

The human microbiome

Collectively, the microorganisms of the human body include an astounding number of bacteria. Since the late 1970s, it has been known that the number of bacterial cells ($\sim 10^{14}$) in and on the human body exceeds the number of human cells ($\sim 10^{13}$) by at least an order of magnitude (Savage, 1977; Peterson et al., 2009; Bianconi et al., 2013). In 2010, it was established that the estimated number

* Corresponding author.
E-mail address: cmlewis@ou.edu (C.M. Lewis).

Ancient Human Microbiomes

- Next Generation Sequencing
- Dental calculus (mineralized bacterial biofilm)

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“There can be no doubt that modern behavior and dietary changes are altering the microbial ecology of humans. While some of these changes could be beneficial, others are disruptive and may be a driving force behind the rapidly increasing rates of chronic inflammatory diseases in developed countries. Common medical interventions, such as antibiotic therapy, have dramatically reduced infectious disease burdens worldwide. However, rather than being targeted strikes against harmful bacteria alone, such therapies can also act as weapons of mass microbial disruption.”

Journal of Human Evolution 79 (2015) 125-136

Hygiene and the world distribution of Alzheimer's Disease

Molly Fox[1,*], Leslie A. Knapp[1,2], Paul W. Andrews[3] and Corey L. Fincher[4]

+ Author Affiliations

* *Corresponding author:* Dr. Molly Fox, Department of Biological Anthropology, University of Cambridge, Pembroke Street, Cambridge CB2 3QY, UK. Tel +44(0)1223 335638, Email mf392@cam.ac.uk

Abstract

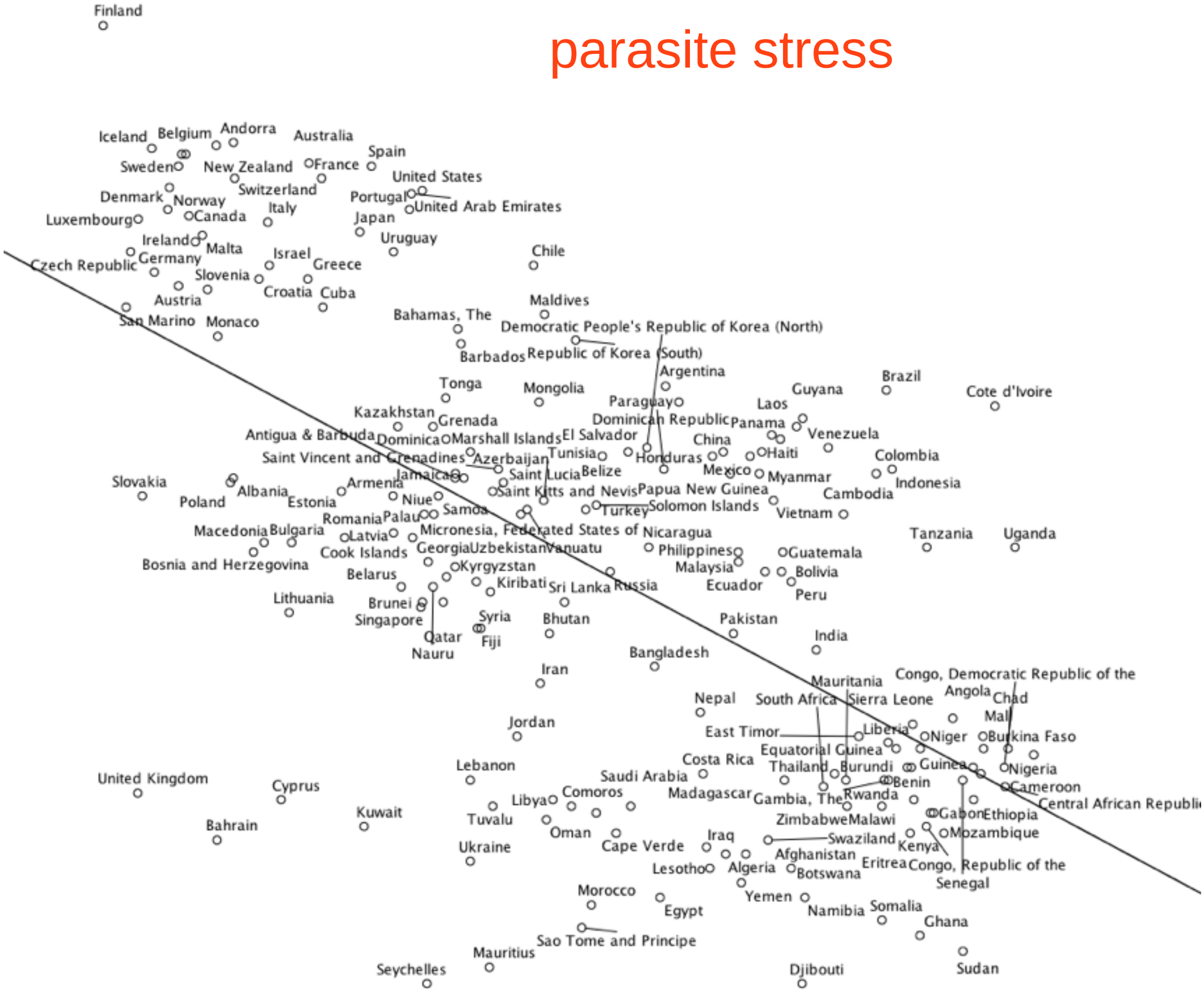
Background and objectives: Alzheimer's Disease (AD) shares certain etiological features with autoimmunity. Prevalence of autoimmunity varies between populations in accordance with variation in environmental microbial diversity. Exposure to microorganisms may improve individuals' immunoregulation in ways that protect against autoimmunity, and we suggest this may also be the case for AD. Here we investigate whether differences in microbial diversity can explain patterns of age-adjusted AD rates between countries.

Hygiene and the world distribution of Alzheimer's Disease

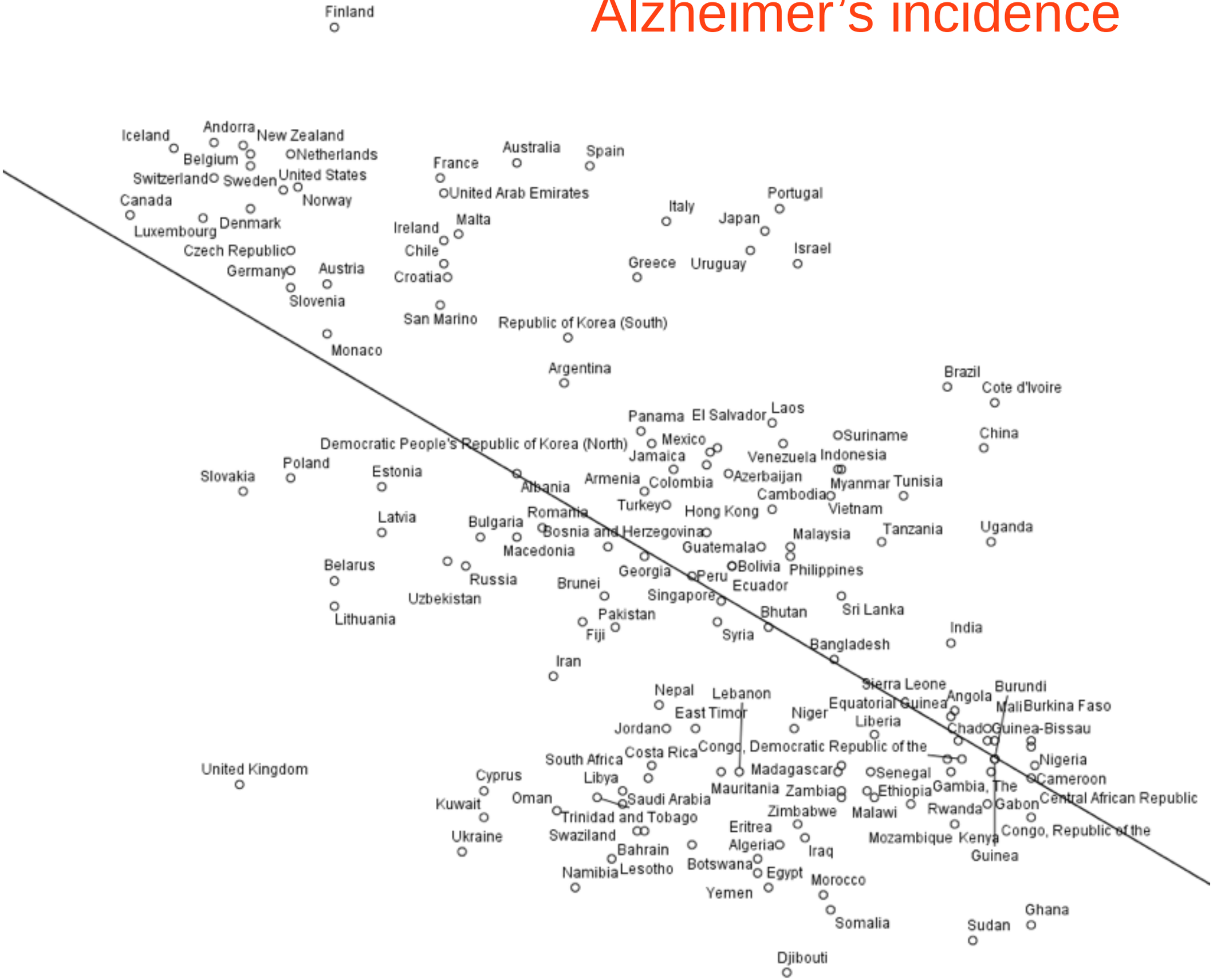
- Epidemiological evidence for a relationship between microbial environment and age-adjusted disease burden
- Comparison to hygiene (parasite load) with Alzheimer's incidence

Evolution, Medicine, and Public Health, August 11, 2013

parasite stress



Alzheimer's incidence



Iceland
Denmark
United States
Japan
Germany
Greece
Austria
China
Poland
Philippines
India
Angola
Iran
Chad
Jordan
Nigeria
Costa Rica
Kuwait
Ethiopia
Kenya
Sudan

Increasing Parasitic Stress

Increasing Alzheimer's Prevalence

Iceland
United States
Denmark
Austria
Germany
Japan
Greece
China
Poland
Philippines
India
Iran
Angola
Chad
Jordan
Nigeria
Ethiopia
Kuwait
Kenya
Sudan
Costa Rica

Increasing Alzheimer's Prevalence

Increasing Parasitic Stress

Iceland
Denmark
Iceland
United States
Japan
Germany
United States
Greece
Denmark
Austria
Austria
Germany
Japan
Greece
China
China
Poland
Poland
Philippines
Philippines
India
India
Angola
Iran
Iran
Chad
Jordan
Jordan
Nigeria
Costa Rica
Ethiopia
Kuwait
Kuwait
Ethiopia
Kenya
Kenya
Sudan
Costa Rica
Sudan

Hygiene and the world distribution of Alzheimer's Disease

Conclusions: Variation in hygiene may partly explain global patterns in AD rates. Microorganism exposure may be inversely related to AD risk. These results may help predict AD burden in developing countries where microbial diversity is rapidly diminishing.

Evolution, Medicine, and Public Health, August 11, 2013

Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications

Molecular and Genetic Medicine

Daulatzai, J Mol Genet Med 2014, S1
http://dx.doi.org/10.4172/1747-0862.S1-005

Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications

Mak Adam Daulatzai*

Sleep Disorders Group, EEE/MSE, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia

Abstract

Obesity, an epidemic problem in the world is associated with several health problems. An understanding of mechanisms/factors that predispose, delay or protect individuals from obesity and its associated metabolic disturbances and cognitive impairment would be invaluable. The human gut harbors a diverse population of microbial organisms which are symbiotic and important for well being. However, studies on conventional and germ-free animals have shown that alteration in normal commensal gut microbiota and an increase in pathogenic microbiome (termed "dysbiosis") contribute to gut inflammation, generation of LPS and pro-inflammatory cytokines, gut leakage, and systemic- and neuro-inflammation. The immune mechanisms that are necessary for gut homeostasis may become dysfunctional and lead to bowel inflammation and gut-brain axis dysfunction. These factors are potentially involved in inducing obesity as well. It may be wise to consider the wider hypothesis that gut's dysbiosis, commencing as a response to fatty food, modulates neuro-inflammation and cognitive dysfunction. This may be enhanced by concomitant noxious factors such as consumption of NSAIDS and alcohol in the elderly. The neurotoxic mechanisms when chronic may enhance vulnerability to dementia of Alzheimer's type (AD), and perhaps contribute to other dementias as well. Therapeutic strategies for amelioration of cognitive decline and AD are desperately needed. It is pragmatic then that immunologically mediated gut dyshomeostasis is abrogated by available options including Prebiotics, Probiotics, and Synbiotics. Decreasing gut's dysbiosis may thus attenuate neuroinflammation and provide a potential treatment for obesity-related cognitive impairment. Further, the 'gut-brain axis' or 'brain-gut axis' (depending on whether one considers bottom-up or top-down pathway) is a bi-directional communication system, comprised of neural pathways encompassing enteric nervous system and the vagus. Vagus nerve stimulation in conjunction with α7 nAChR agonists may be an important therapeutic modality in gut pathology to upregulate parasympathetic/vagal efferent function, ameliorate gut-brain axis dysfunction and neuroinflammation, and decrease vulnerability to AD.

Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications

- Obesity is associated with inflammation
- Obesity is associated with hippocampal atrophy
- Obesity is associated with cognitive decline

J Mol Genet Med 2014, S1

ORIGINAL CONTRIBUTION

Central Obesity and the Aging Brain

William Jagust, MD; Danielle Harvey, PhD; Dan Mungas, PhD; Mary Haan, DrPH

Background: Central adiposity as an indicator of visceral fat is linked to vascular and metabolic factors that in turn are related to cognitive decline and dementia.

Objective: To determine whether larger waist-hip ratio (WHR) is associated with structural brain changes that underlie cognitive decline and dementia.

Design: Cross-sectional analysis of an epidemiologic cohort study of cognitive and functional decline (Sacramento Area Latino Study on Aging).

Setting: California Central Valley.

Participants: A total of 112 individuals selected from an ongoing cohort study of 1789 older Latino individuals. Baseline anthropomorphic measures (WHR) and measurements of fasting blood glucose, cholesterol, and insulin levels and blood pressure were obtained.

Main Outcome Measures: Baseline magnetic resonance images were analyzed quantitatively to determine the hippocampal volumes in the right and left hemispheres and rated for the percentage of white matter hyperintensities.

Results: Greater WHR ($P=.02$) and older age ($P<.001$) were negatively related to hippocampal volumes. The WHR and age were positively related to white matter hyperintensities ($P=.02$ and $P=.001$, respectively). A 1-SD increase in WHR was associated with a 0.2-SD decrease in hippocampal volume and a 27% increase in white matter hyperintensities. These relationships were not affected by adjustment for body mass index, total cholesterol, fasting blood glucose, and insulin levels or systolic blood pressure in the models.

Conclusion: A larger WHR may be related to neurodegenerative, vascular, or metabolic processes that affect brain structures underlying cognitive decline and dementia.

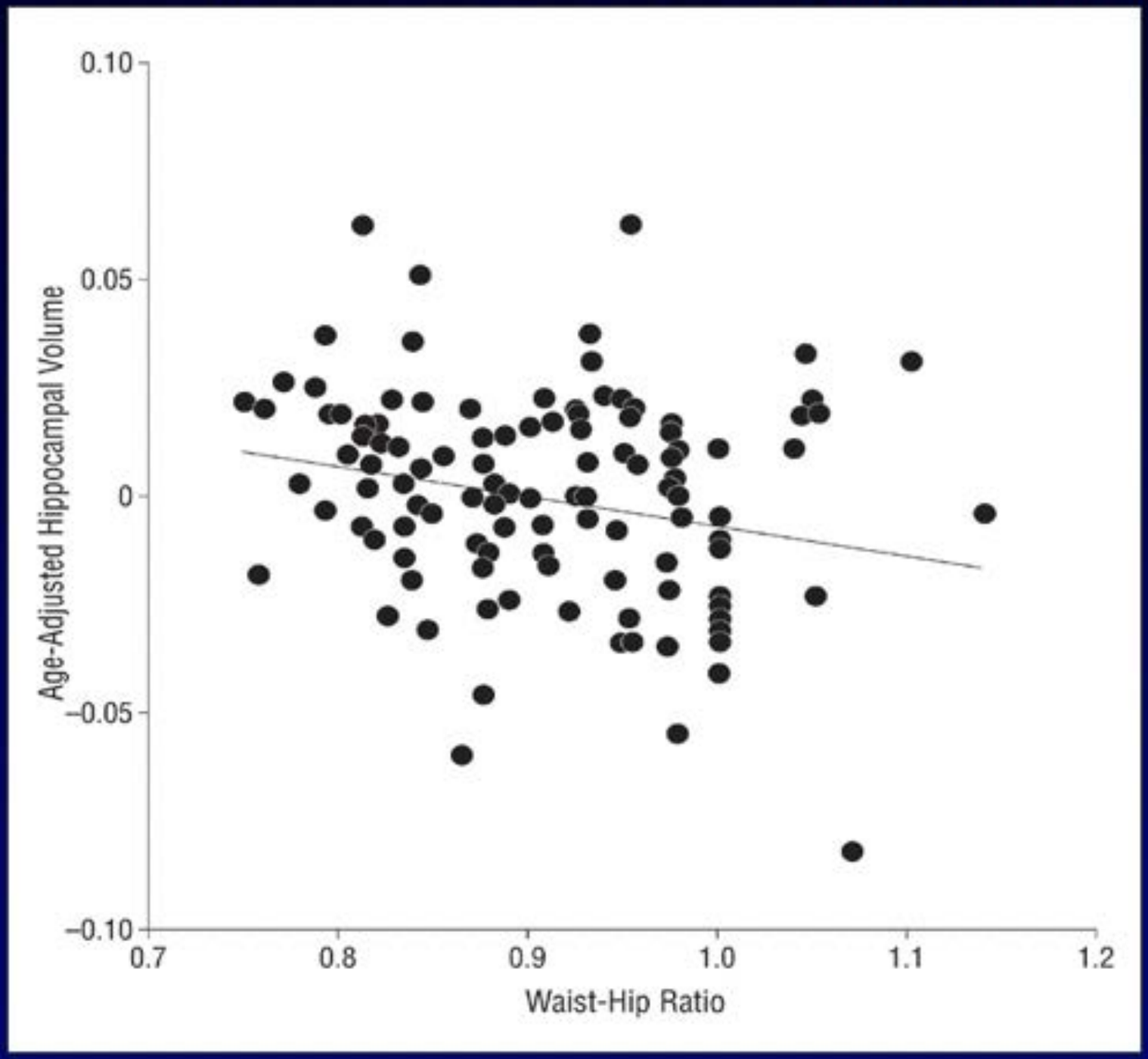
Arch Neurol. 2005;62:1545-1548

Central Obesity and the Aging Brain

Jagust. W., et al., Arch Neurol 62: 1545-48; October, 2005

- 112 older Latinos
- Waist to Hip Ratio
- Volumetric MRI of hippocampus

Plot of waist-hip ratio vs age-adjusted hippocampal volume



Jagust, W. et al. Arch Neurol 2005; 62:1545-1548

Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications

- Obesity is associated with **dysbiosis**

J Mol Genet Med 2014, S1

"This may be enhanced by concomitant noxious factors such as consumption of NSAIDS."

dysbiosis

gut inflammation

increased gut permeability

translocation of LPS

pro-inflammatory cytokines

neuro-inflammation

dysbiosis

gut inflammation

increased gut permeability

translocation of LPS

pro-inflammatory cytokines

neuro-inflammation

Zonis et al. Journal of Neuroinflammation (2015) 12:65
DOI 10.1186/s12974-015-0281-0

JOURNAL OF NEUROINFLAMMATION

RESEARCH Open Access

Chronic intestinal inflammation alters hippocampal neurogenesis

Svetlana Zonis[1], Robert N Pechnick[3], Vladimir A Ljubimov[1], Michael Mahgerefteh[1], Kolja Wawrowsky[1], Kathrin S Michelsen[2] and Vera Chesnokova[1*]

Abstract

Background: Adult neurogenesis in the subgranular zone of the hippocampus is involved in learning, memory, and mood control. Decreased hippocampal neurogenesis elicits significant behavioral changes, including cognitive impairment and depression. Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the intestinal tract, and cognitive dysfunction and depression frequently occur in patients suffering from this disorder. We therefore tested the effects of chronic intestinal inflammation on hippocampal neurogenesis.

Methods: The dextran sodium sulfate (DSS) mouse model of IBD was used. Mice were treated with multiple-cycle administration of 3% wt/vol DSS in drinking water on days 1 to 5, 8 to 12, 15 to 19, and 22 to 26. Mice were sacrificed on day 7 (acute phase of inflammation) or day 29 (chronic phase of inflammation) after the beginning of the treatment.

Results: During the acute phase of inflammation, we found increased plasma levels of IL-6 and TNF-α and increased expression of Iba1, a marker of activated microglia, accompanied by induced IL-6 and IL-1β, and the cyclin-dependent kinase inhibitor $p21^{Cip1}$ (p21) in hippocampus. During the chronic phase of inflammation, plasma levels of IL-6 were elevated. In the hippocampus, p21 protein levels were continued to be induced. Furthermore, markers of stem/early progenitor cells, including nestin and brain lipid binding protein (BLBP), and neuronal marker doublecortin (DCX) were all down-regulated, whereas glial fibrillary acidic protein (GFAP), a marker for astroglia, was induced. In addition, the number of proliferating precursors of neuronal lineage assessed by double Ki67 and DCX staining was significantly diminished in the hippocampus of DSS-treated animals, indicating decreased production of new neurons.

Conclusions: We show for the first time that chronic intestinal inflammation alters hippocampal neurogenesis. As p21 arrests early neuronal progenitor proliferation, it is likely that p21 induction during acute phase of inflammation resulted in the reduction of hippocampal neurogenesis observed later, on day 29, after the beginning of DSS treatment. The reduction in hippocampal neurogenesis might underlie the behavioral manifestations that occur in patients with IBD.

Keywords: Inflammatory bowel disease, Chronic peripheral inflammation, Hippocampus, Adult neurogenesis, p21

Chronic intestinal inflammation alters hippocampal neurogenesis

Adult neurogenesis in the hippocampus is involved in learning, memory, and mood control. Decreased hippocampal neurogenesis elicits significant behavioral changes, including cognitive impairment and depression.

Journal of Neuroinflammation (2015) 12:65

Chronic intestinal inflammation alters hippocampal neurogenesis

Dextran sodium sulfate (DSS) added to drinking water. Animals sacrificed day 7 and 29 (acute and chronic phases of inflammation)

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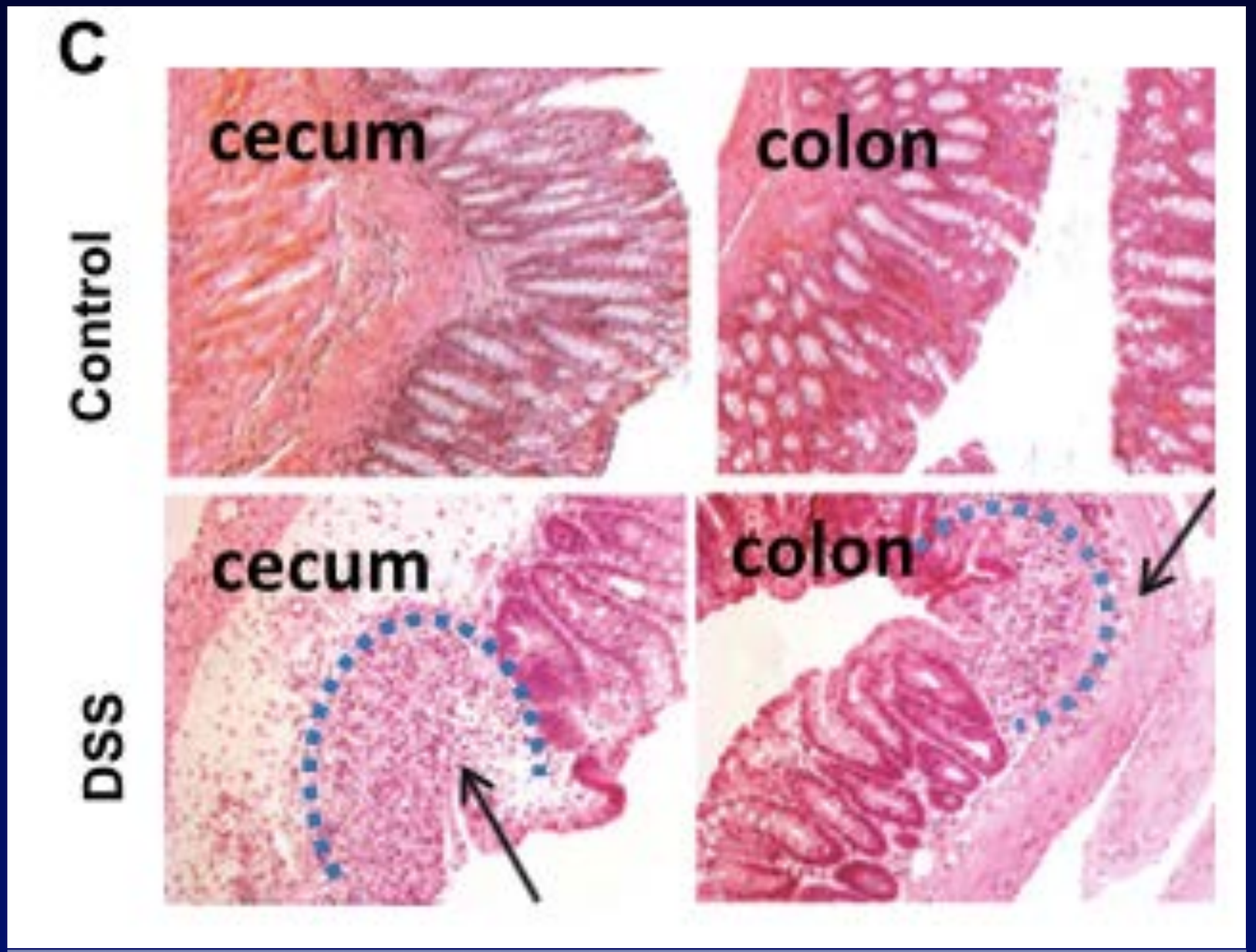
Day 29 after DSS administration



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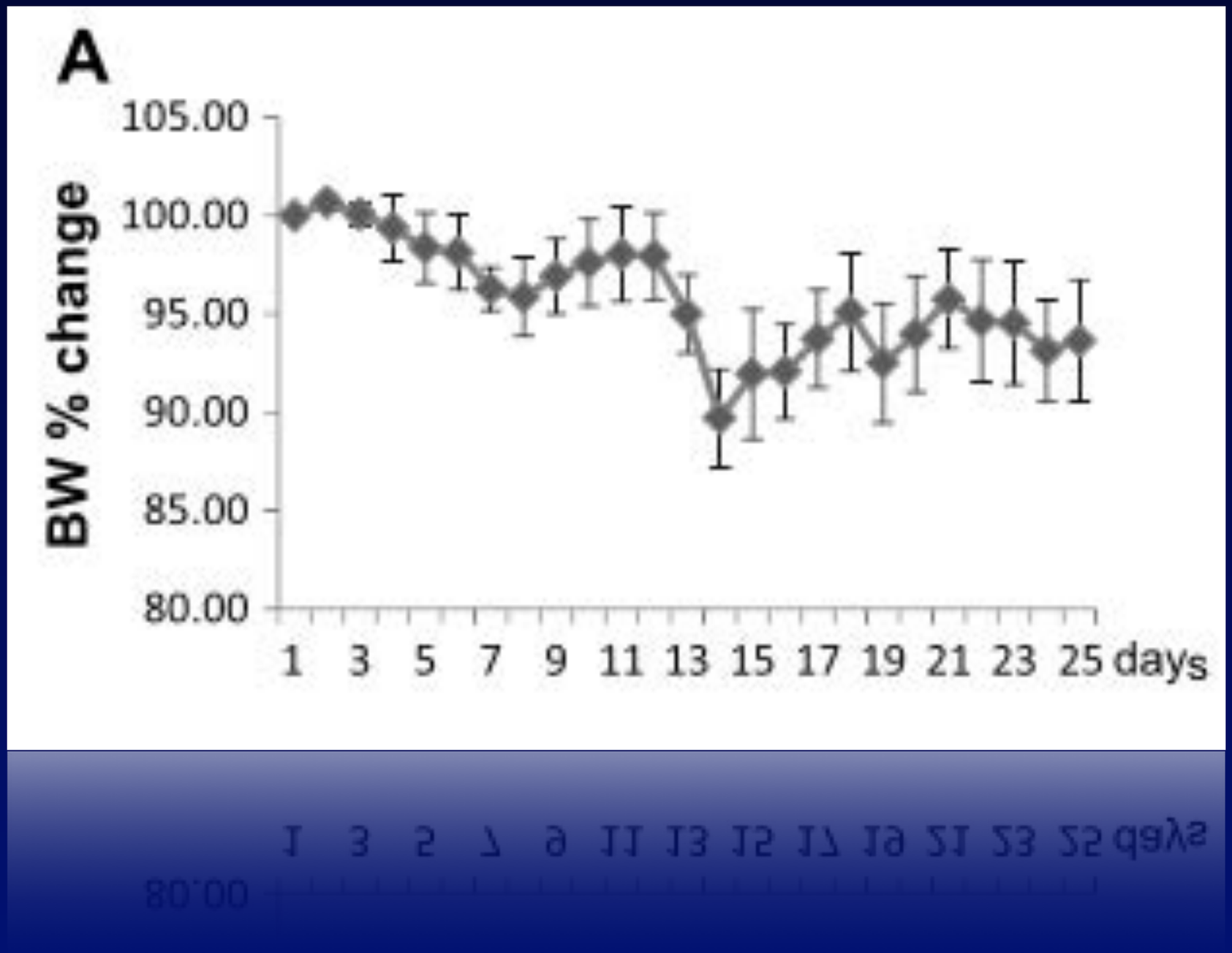
Day 29 after DSS administration



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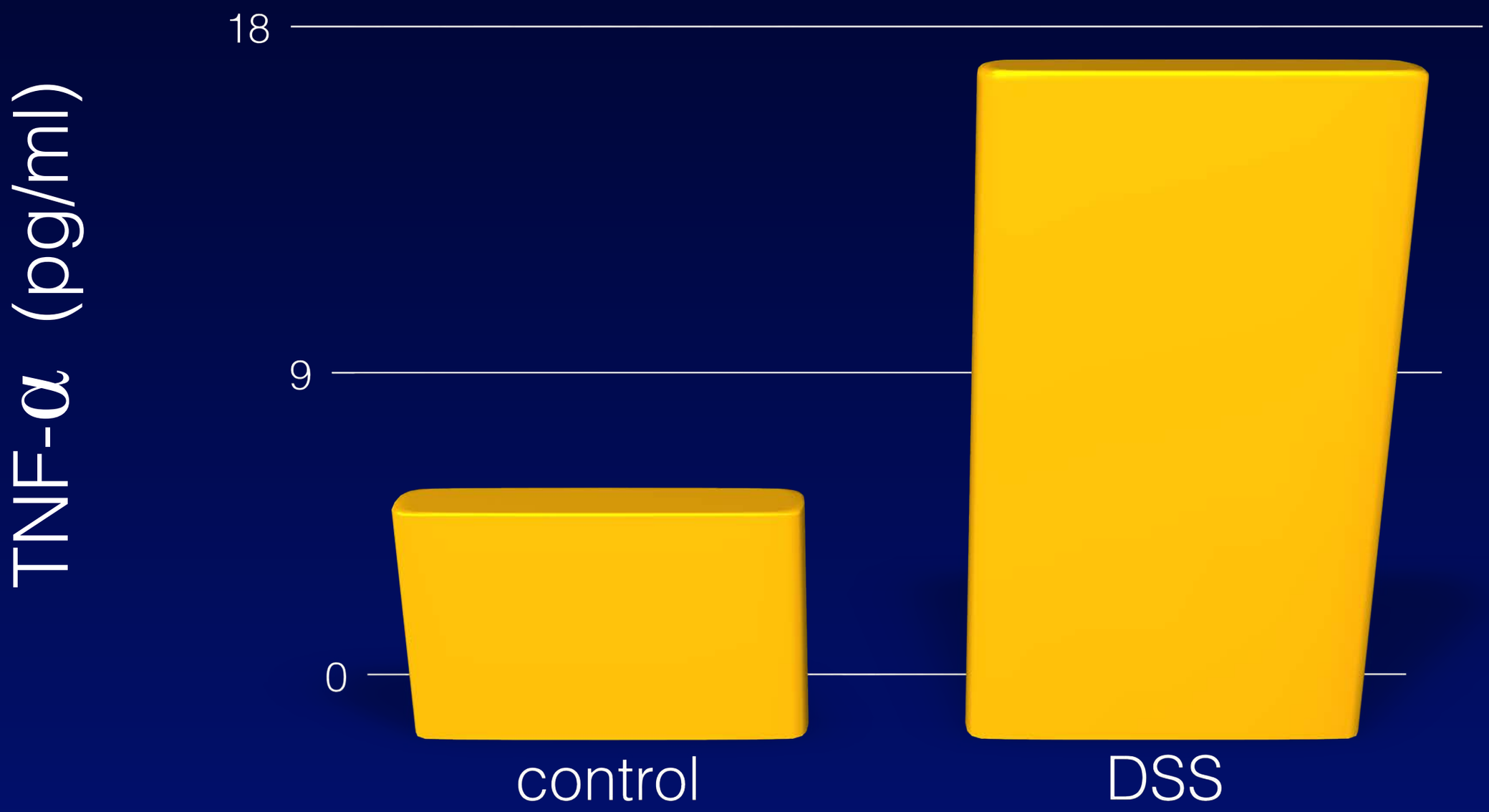
Day 29 after DSS administration



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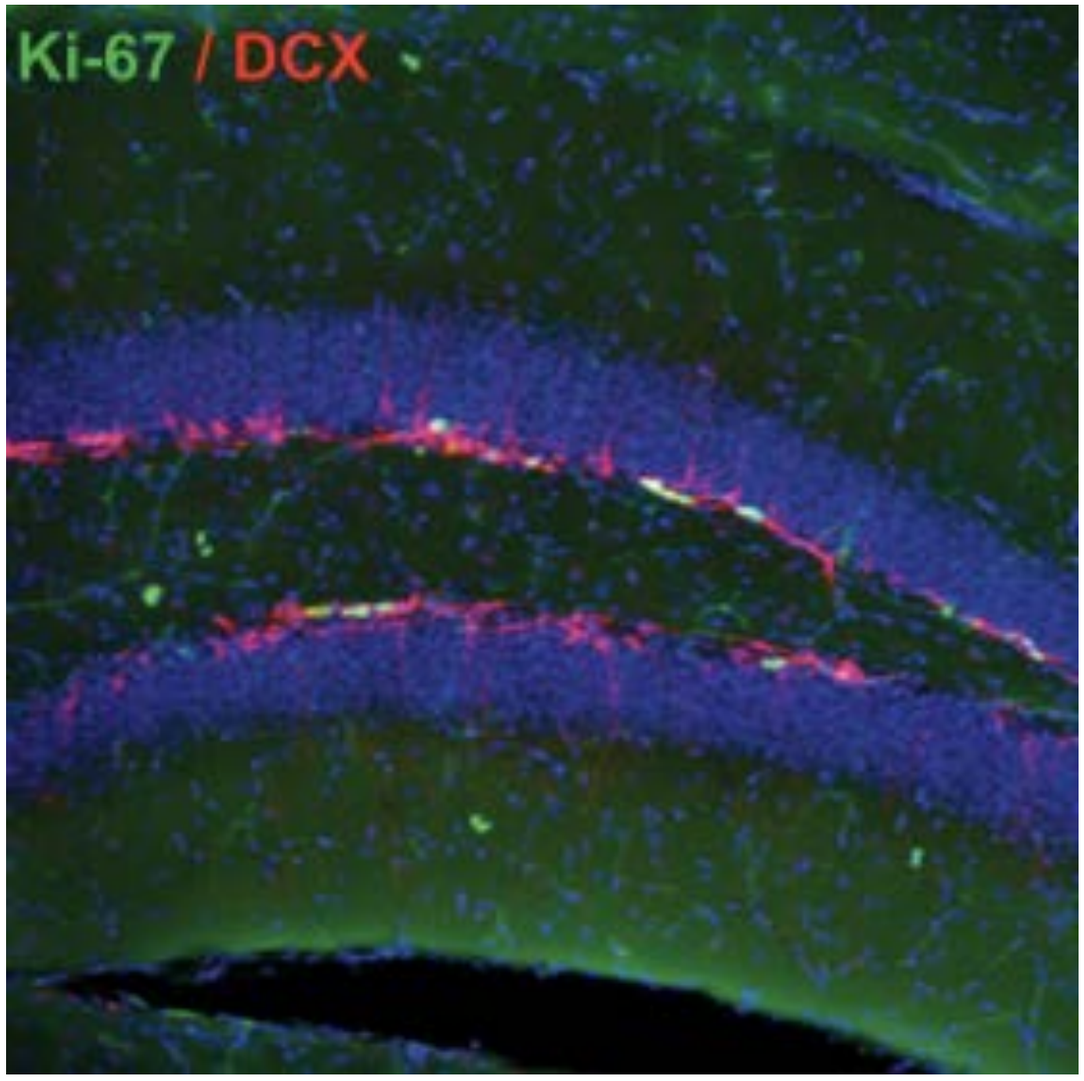
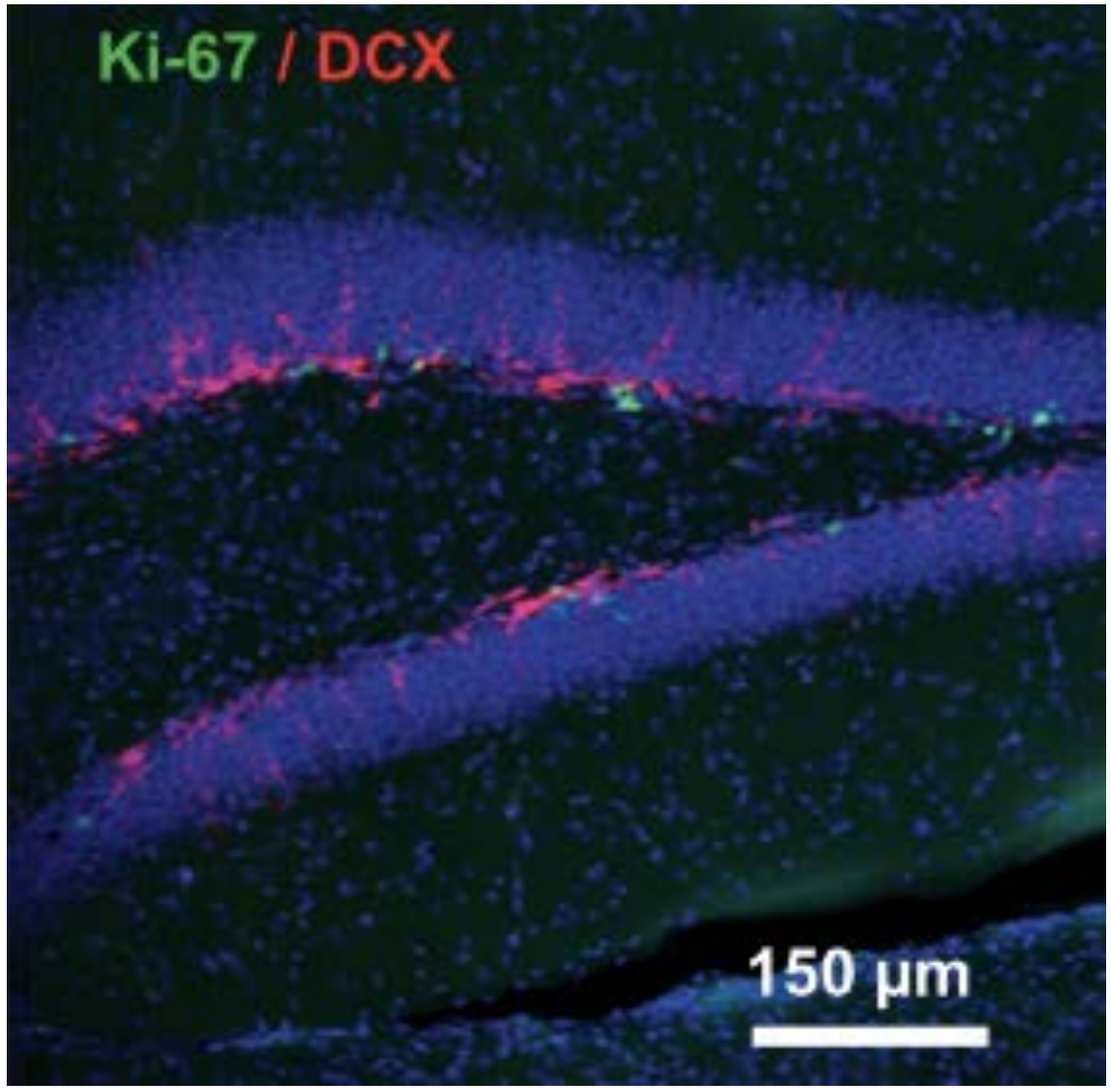
Day 29 after DSS administration



control



DSS

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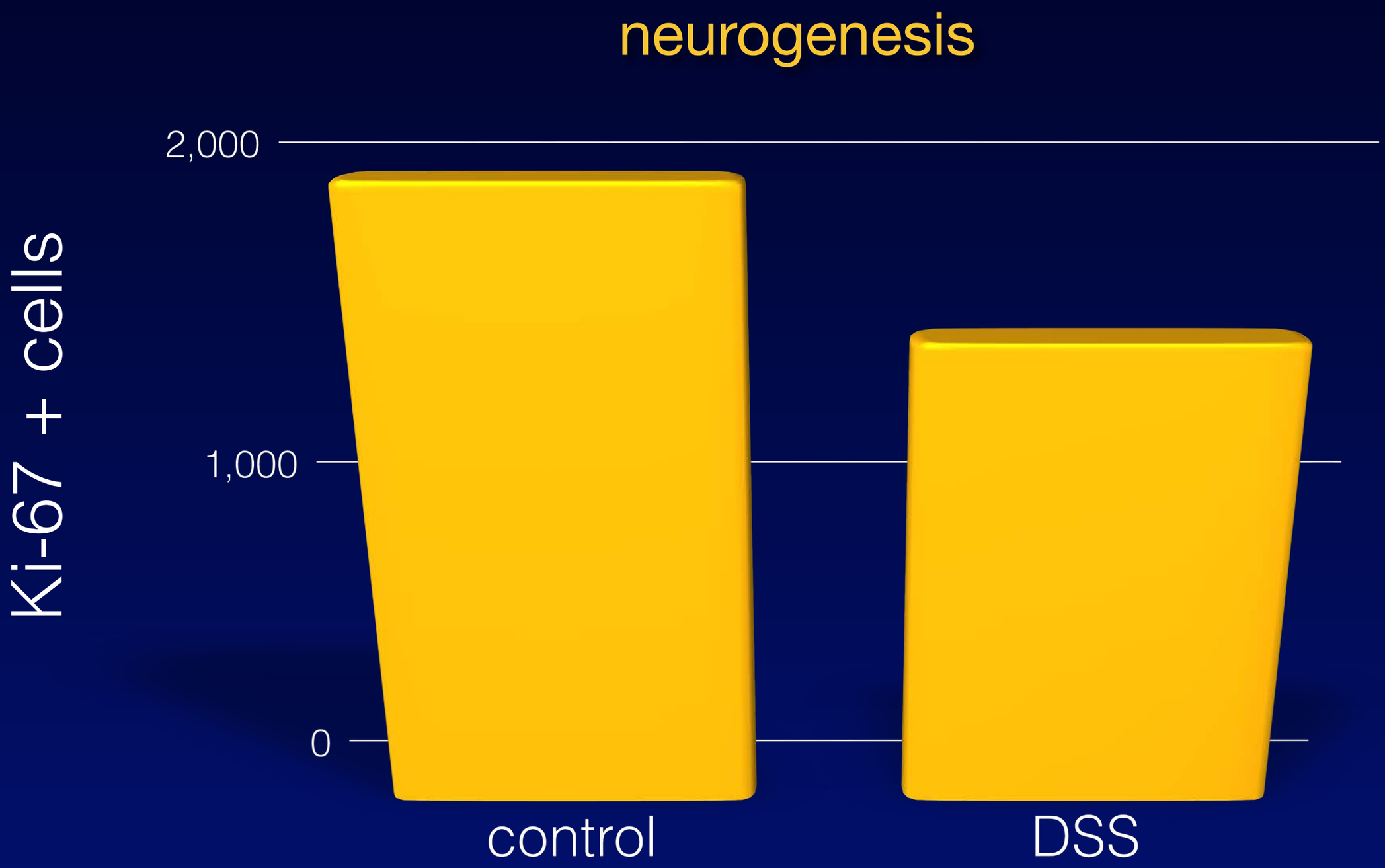
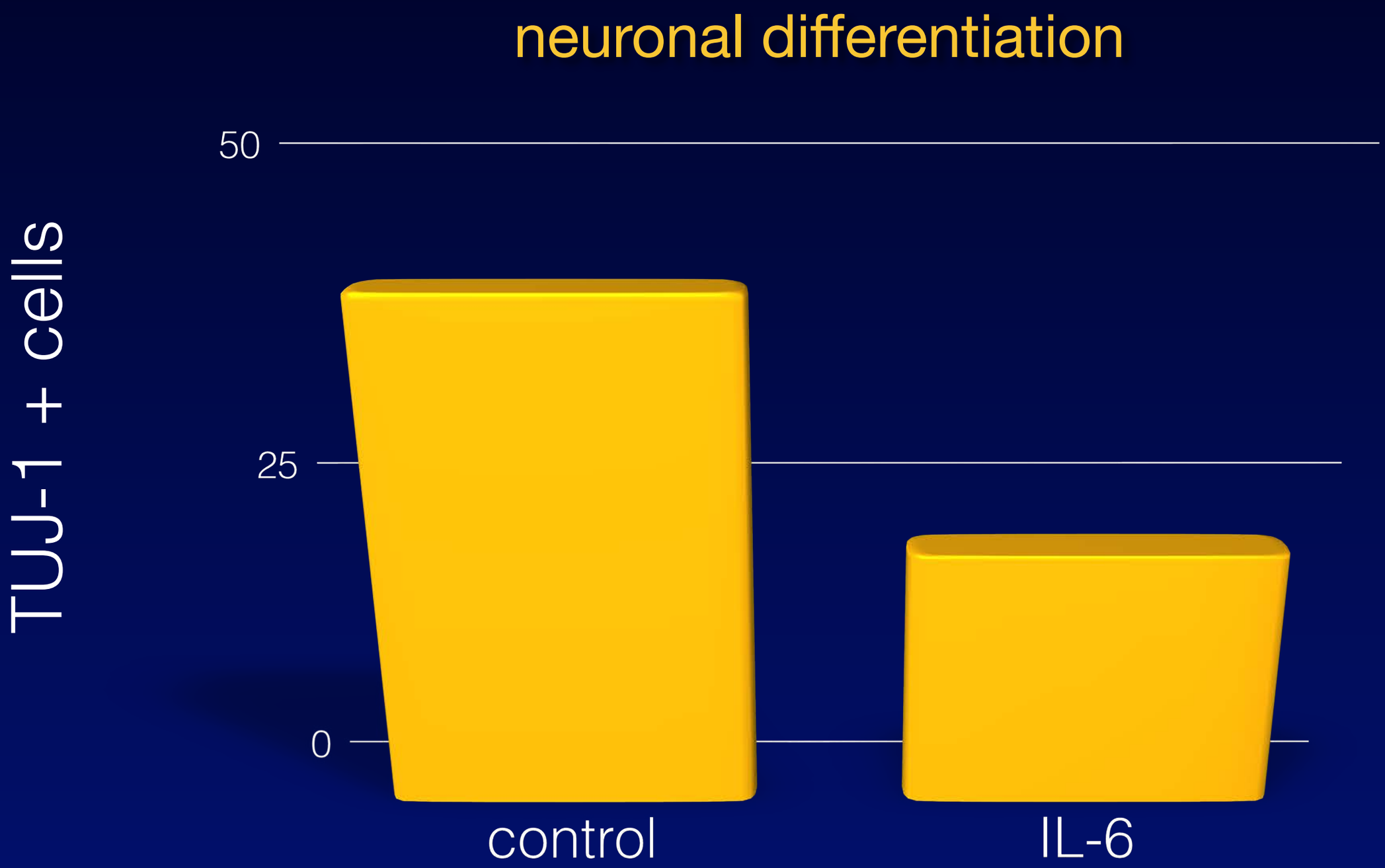
Day 29 after DSS administration



Journal of Neuroinflammation (2015) 12:65

In vitro IL-6 administration (50ng/ml)



Journal of Neuroinflammation (2015) 12:65

Chronic intestinal inflammation alters hippocampal neurogenesis

Chronic intestinal inflammation suppresses hippocampal neurogenesis. Increased levels of proinflammatory cytokines have detrimental effects on proliferation of progenitors of neuronal lineage. Deficient hippocampal neurogenesis may underlie increased rate of mood disorder and cognitive impairment observed in IBD patients.

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Journal of Neuroinflammation (2015) 12:65

- Antibiotics
- Method of delivery
- Medications
- Water treatment
- Diet
- Hormone therapy
- GMO

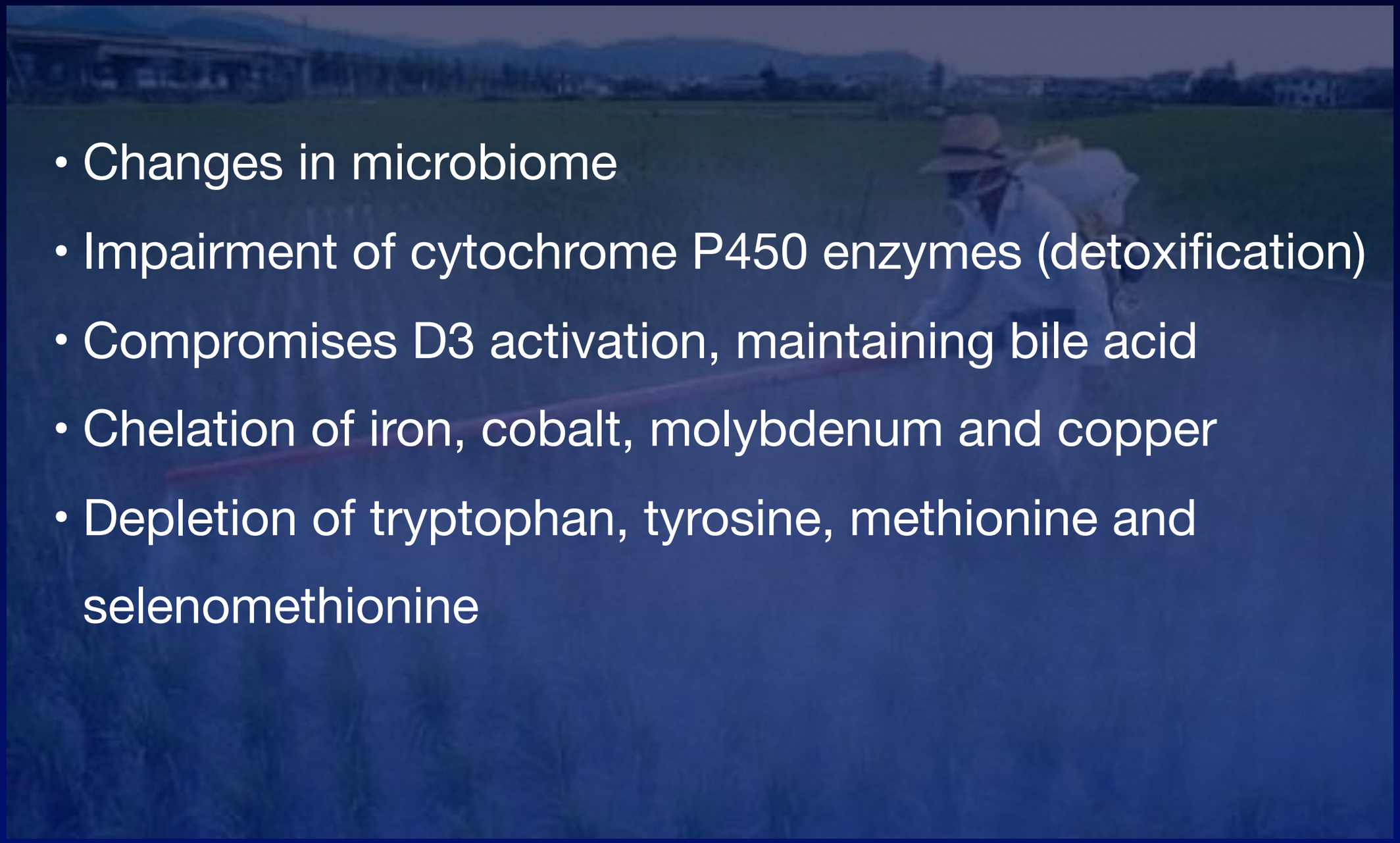
Global Glyphosate Market to Reach 1.35 Million Metric Tons by 2017, According to a New Report by Global Industry Analysts, Inc.

G… growing adoption/planting of glyphosate-ready n

G Genetically Modified crops,

m…illion metric tons by the year 2017+ major factors driving growth in the global glyphosate market include lack of a substitution to glyphosate, growing adoption/planting of glyphosate-ready Genetically Modified (GM) crops, rising use of no-till or minimum-till systems, and expected increase in bio-fuel projects in several countries worldwide.

Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance



- Changes in microbiome
- Impairment of cytochrome P450 enzymes (detoxification)
- Compromises D3 activation, maintaining bile acid
- Chelation of iron, cobalt, molybdenum and copper
- Depletion of tryptophan, tyrosine, methionine and selenomethionine

Interdiscip Toxicol. 2013; **Vol. 6**(4): 159–184

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.[1]

The insecticides tetrachlorvinphos and parathion were classified as "possibly carcinogenic to humans" (Group 2B). The evidence from human studies was scarce and considered inadequate. Tetrachlorvinphos induced hepatocellular tumours (benign or malignant) in mice, renal tubule tumours (benign or malignant) in male mice,[2] and spleen haemangioma in male rats. Tetrachlorvinphos is a reactive oxon with affinity for esterases. In experimental animals, tetrachlorvinphos is systemically distributed, metabolised, and eliminated in urine. Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and in vitro) and increased cell proliferation (hyperplasia in rodents). Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars.

For parathion, associations with cancers in several tissues were observed in occupational studies, but the evidence in humans remains sparse. In mice, parathion increased bronchiolo-alveolar adenoma and/or carcinoma in males, and lymphoma in females. In rats, parathion induced adrenal cortical adenoma or carcinoma (combined),[3] malignant pancreatic tumours, and thyroid follicular cell adenoma in males, and mammary gland adenocarcinoma (after subcutaneous injection in females).[4] Parathion is rapidly absorbed and distributed. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.[4] Parathion use has been severely restricted since the 1980s.

The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses of occupational exposures reported positive associations with non-Hodgkin lymphoma in the USA,[5] Canada,[6] and Sweden,[7] although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study[8] and in the AHS, which reported a significant trend for aggressive cancers after adjustment for other pesticides.[9] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[10] In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.[4] Malathion is rapidly absorbed and distributed. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malaoxon strongly inhibits esterases; atropine reduced carcinogenesis-related effects in one study.[4] Malathion induced DNA and chromosomal damage in humans, corroborated by studies in animals and in vitro. Bacterial mutagenesis tests were negative. Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation.

Diazinon has been applied in agriculture and for control of home and garden insects. There was limited evidence for diazinon carcinogenicity in humans. Positive associations for non-Hodgkin lymphoma, with

Lancet Oncol 2015

Published Online March 20, 2015 http://dx.doi.org/10.1016/S1470-2045(15)70134-8

For more on the IARC Monographs see http://monographs.iarc.fr

Upcoming meetings

June 2–9, 2015, Volume 113: Some organochlorine insecticides and some chlorphenoxy herbicides

Oct 6–13, 2015, Volume 114: Red meat and processed meat

Monograph Working Group Members

A Blair (USA)—Meeting Chair; L Fritschi (Australia); J McLaughlin; C M Sergi (Canada); G M Calaf (Chile); F Le Curieux (Finland); I Baldi (France); F Forastiere (Italy); H Kromhout (Netherlands); A 't Mannetje (New Zealand); T Rodriguez [unable to attend] (Nicaragua); P Egeghy [unable to attend]

	Activity (current status)	Evidence in humans (cancer sites)	Evidence in animals	Mechanistic evidence	Classification*
Tetrachlorvinphos	Insecticide (restricted in the EU and for most uses in the USA)	Inadequate	Sufficient	–	2B
Parathion	Insecticide (restricted in the USA and EU)	Inadequate	Sufficient	–	2B
Malathion	Insecticide (currently used; high production volume chemical)	Limited (non-Hodgkin lymphoma, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A†
Diazinon	Insecticide (restricted in the USA and EU)	Limited (non-Hodgkin lymphoma, leukaemia, lung)	Limited	Genotoxicity and oxidative stress	2A†
Glyphosate	Herbicide (currently used; highest global production volume herbicide)	Limited (non-Hodgkin lymphoma)	Sufficient	Genotoxicity and oxidative stress	2A†

EU=European Union. *See the International Agency for Research on Cancer (IARC) preamble for explanation of classification system (amended January, 2006). †The 2A classification of diazinon was based on limited evidence of carcinogenicity in humans and experimental animals, and strong mechanistic evidence; for malathion and glyphosate, the mechanistic evidence provided independent support of the 2A classification based on evidence of carcinogenicity in humans and experimental animals.

Table: IARC classification of some organophosphate pesticides

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

The Lancet, March 20, 2015

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

> “Glyphosate is a broad-spectrum herbicide, currently with the highest production volumes of all herbicides. It is used in more than 750 different products for agriculture, forestry, urban, and home applications.”

The Lancet, March 20, 2015

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

The Working Group classified glyphosate as "probably carcinogenic to humans."

The Lancet, March 20, 2015

It is an antibiotic.

Glyphosate formulations and their use for the inhibition of 5-enolpyruvylshikimate-3-phosphate synthase

US 7771736 B2

Publication number	US7771736 B2
Publication type	Grant
Application number	US 10/652,684
Publication date	Aug 10, 2010
Filing date	Aug 29, 2003
Priority date ⓘ	Aug 30, 2002
Fee status ⓘ	Paid
Also published as	US20040077608
Inventors	William Abraham
Original Assignee	Monsanto Technology Llc
Export Citation	BiBTeX, EndNote, RefMan

Patent Citations (4), Non-Patent Citations (15), Classifications (17), Legal Events (3)

External Links: USPTO, USPTO Assignment, Espacenet

ABSTRACT

Protozoan parasites of the phylum Apicomplexa include some of the most important causative agents of human and animal diseases, in particular, malaria. The discovery that an organelle found inside parasites of this phylum probably stems from a plastid of plant origin has stimulated research on the effect of chemical herbicidal agents on Apicomplexa. Importantly, the growth of these parasites can be inhibited by the herbicide glyphosate, suggesting that the shikimate pathway will make a good target for the development of new anti-parasite agents. The present invention discloses the use of the herbicidal agent glyphosate in combination with the polyvalent anion oxalic acid for the prevention and therapy of these pathogenic infections.

Threaten microbial diversity

- Antibiotics
- Method of delivery
- Medications
- Water treatment
- Diet
- Hormone therapy
- GMO

inflammation

leading to increased gut permeability

Inflammation

- Alzheimer’s disease
- Parkinson’s disease
- Autism
- Multiple sclerosis
- Stroke
- Depression
- ADHD

Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Reduced diversity - autoimmune, metabolic, and inflammatory diseases

Microbiome. August 8, 2016. 4:42

Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

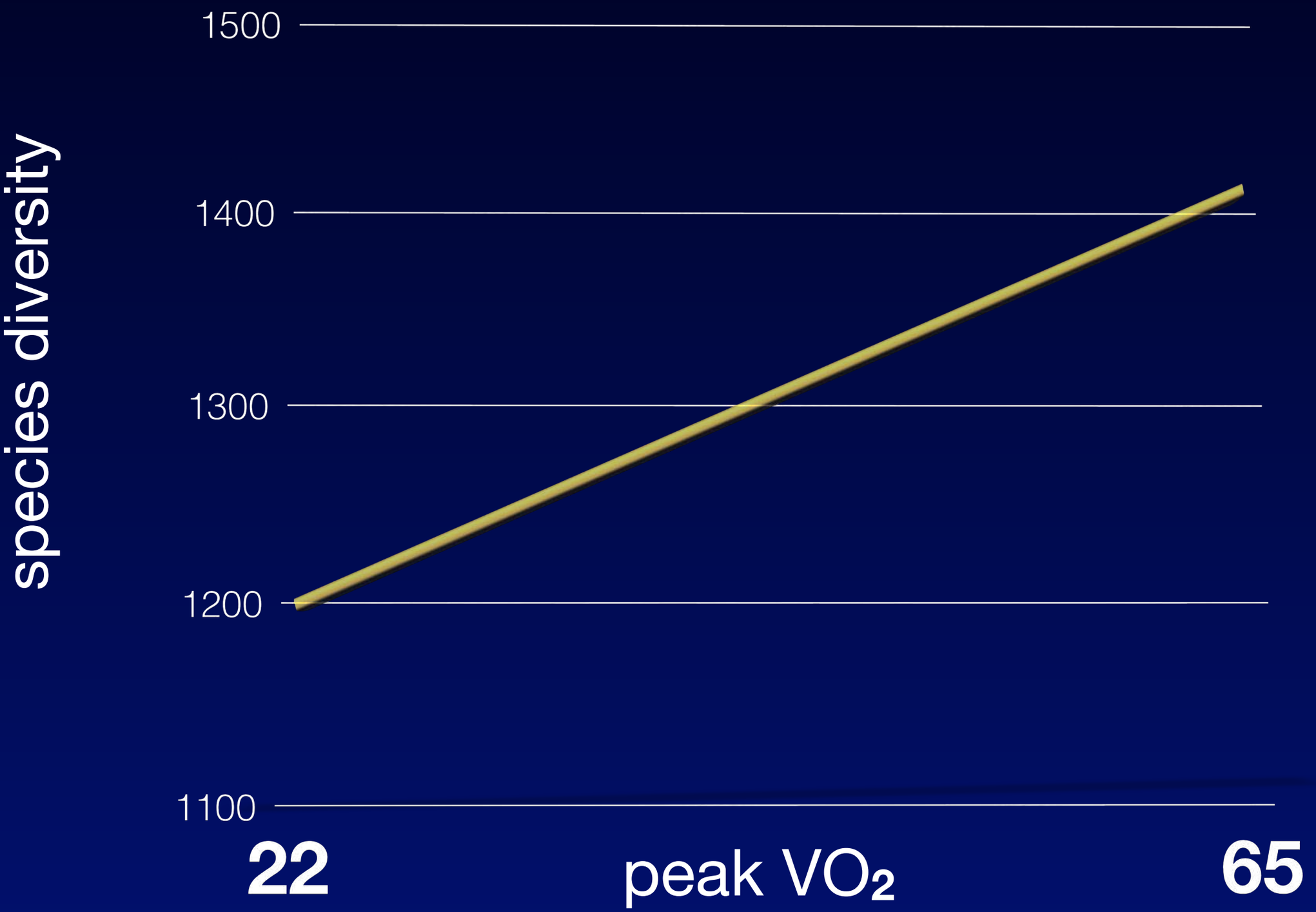
- Diabetes (types 1 and 2), obesity, Alzheimer's, MS, autism, colorectal cancer, inflammatory bowel disease.

Microbiome. August 8, 2016. 4:42

Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Analysis of fecal microbiota of 39 healthy participants with similar age, BMI, and diets but with varying cardiorespiratory fitness levels.
- Correlated with peak oxygen uptake (VO_2 peak), the gold standard measure of cardiorespiratory fitness.

Microbiome. August 8, 2016. 4:42



Microbiome. August 8, 2016. 4:42

Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- Our regression model showed that ~20 % of variation in gut bacterial alpha diversity could be explained by VO_2 peak alone; in fact, VO_2 peak stood as the *only* variable that significantly contributed to increased alpha diversity. The primary findings from this study suggest that cardiorespiratory fitness is a good predictor of gut microbial diversity in healthy humans, outperforming several other variables including sex, age, BMI, and dietary components.

Microbiome. August 8, 2016. 4:42

Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions

- The microbiome in high cardiorespiratory fitness individuals seems to favor a decreased LPS biosynthetic pathways. In addition, a strong positive correlation was observed between VO_2 peak and fecal butyric acid, a SCFA associated with gut health.

Microbiome. August 8, 2016. 4:42

Threaten microbial diversity

- Antibiotics
- Method of delivery
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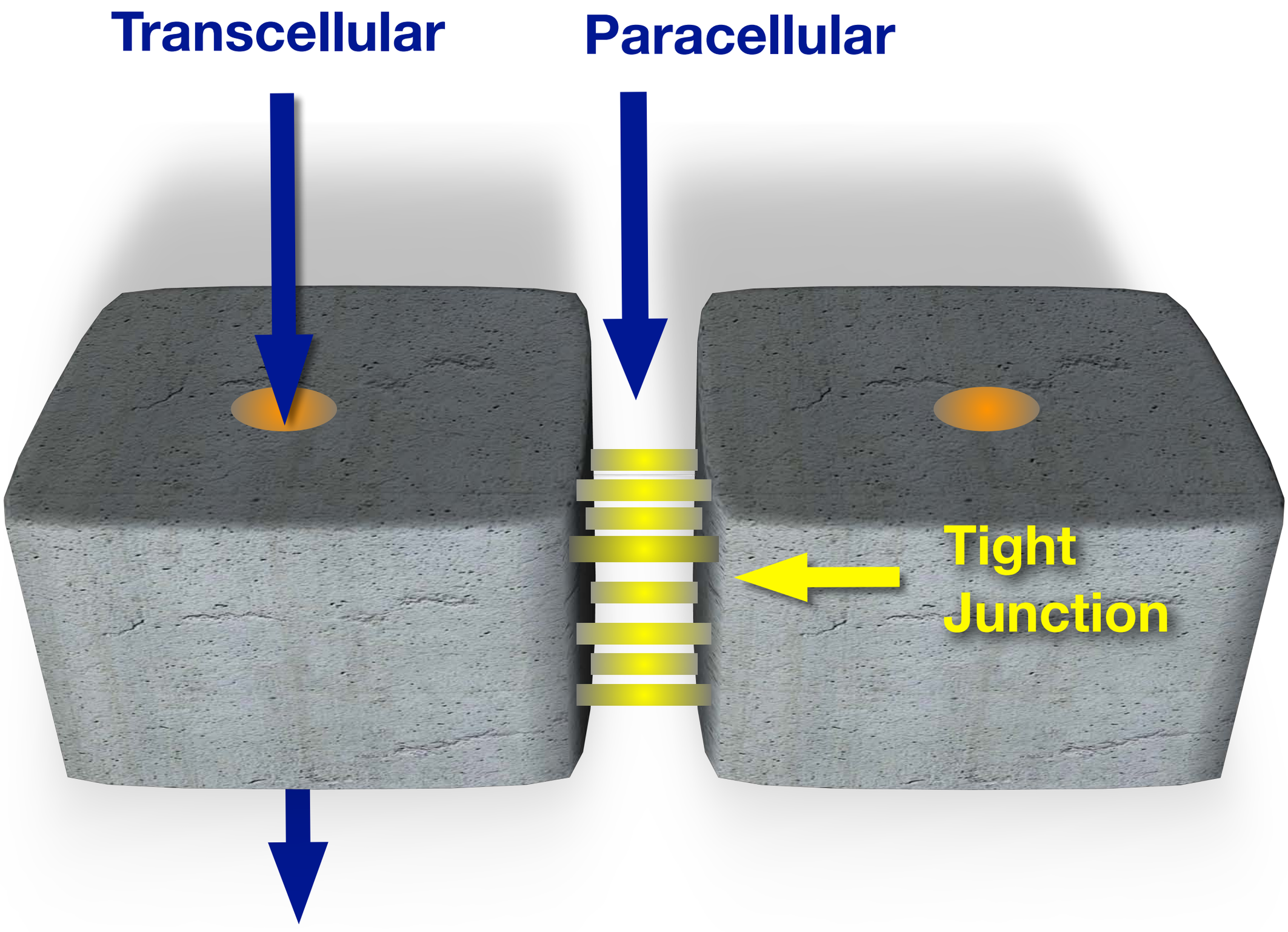
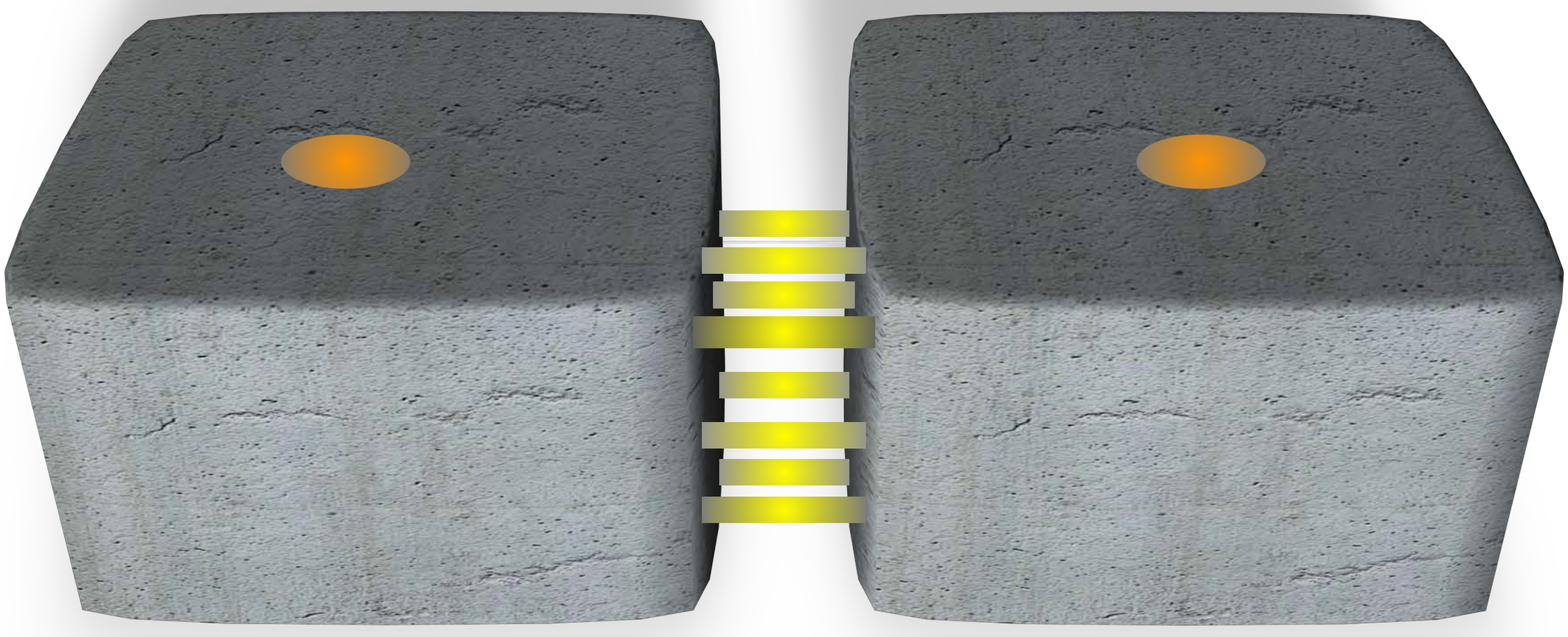
- Water treatment
- Diet
- Hormone therapy
- GMO

leading to increased gut permeability

Intestinal epithelium - absorption pathways

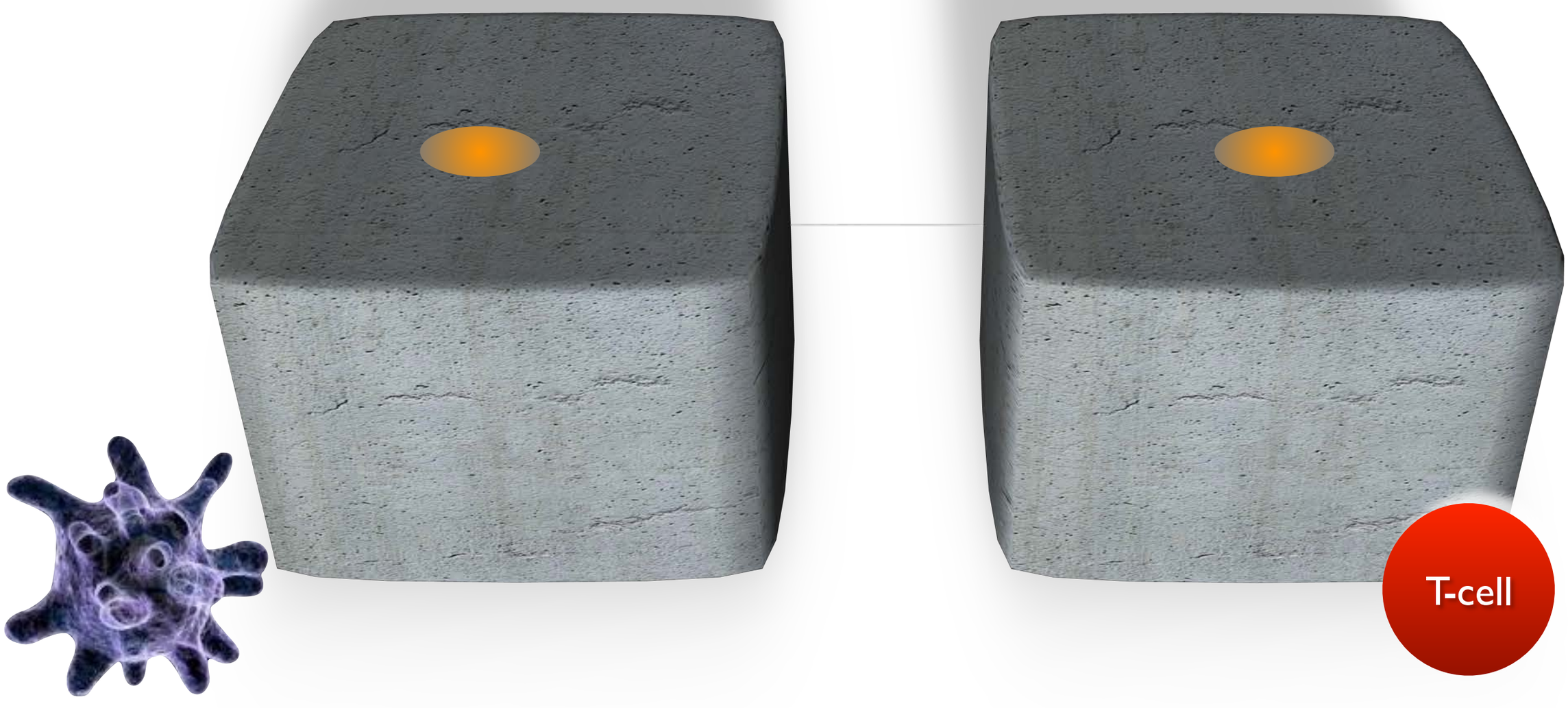


- **stress**
- **infection**
- **drugs**
- **xenobiotics**
- **gliadin**
- **AGEs**



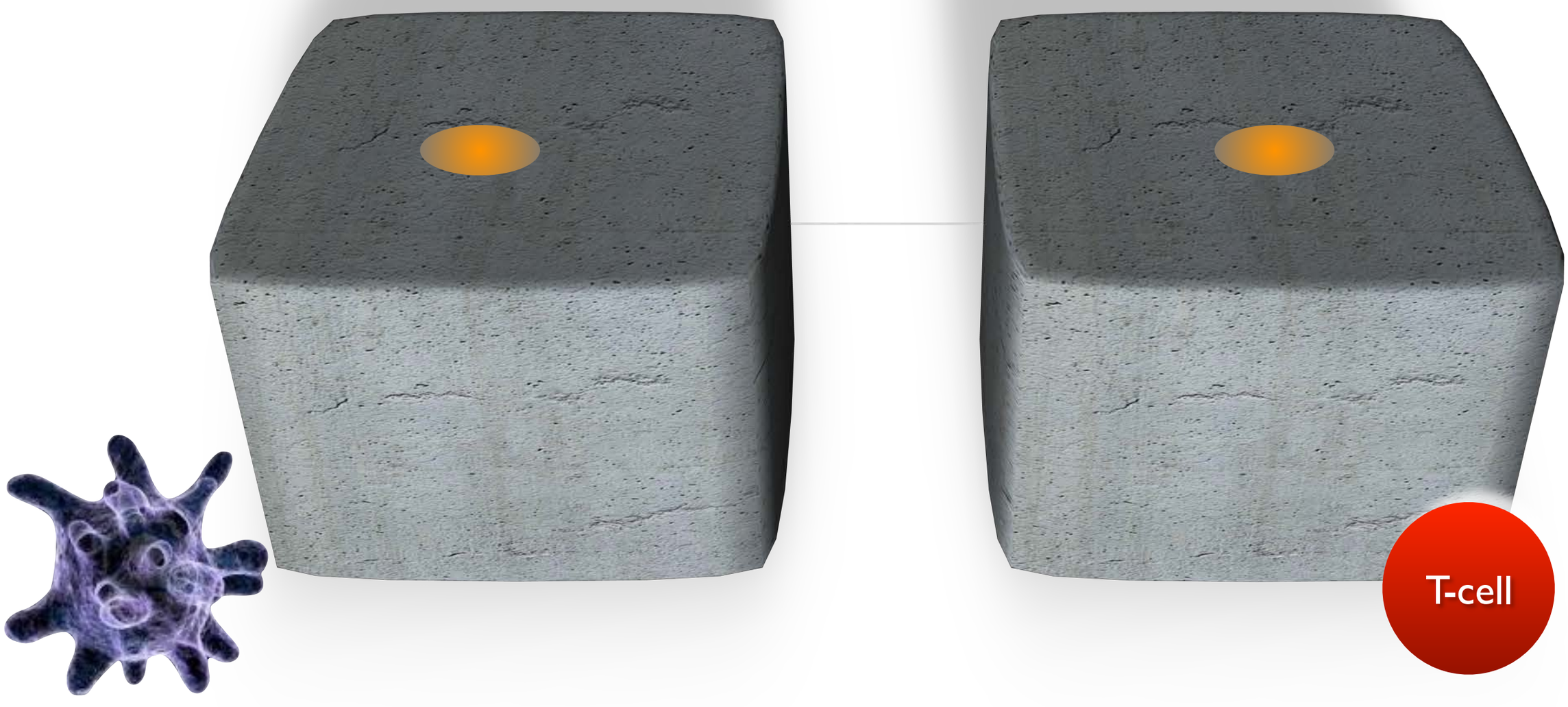
entry of LPS and food antigens into circulation

inflammation



LPS

Lipopolysaccaride (endotoxin) on cell membrane of gram (-) bacteria



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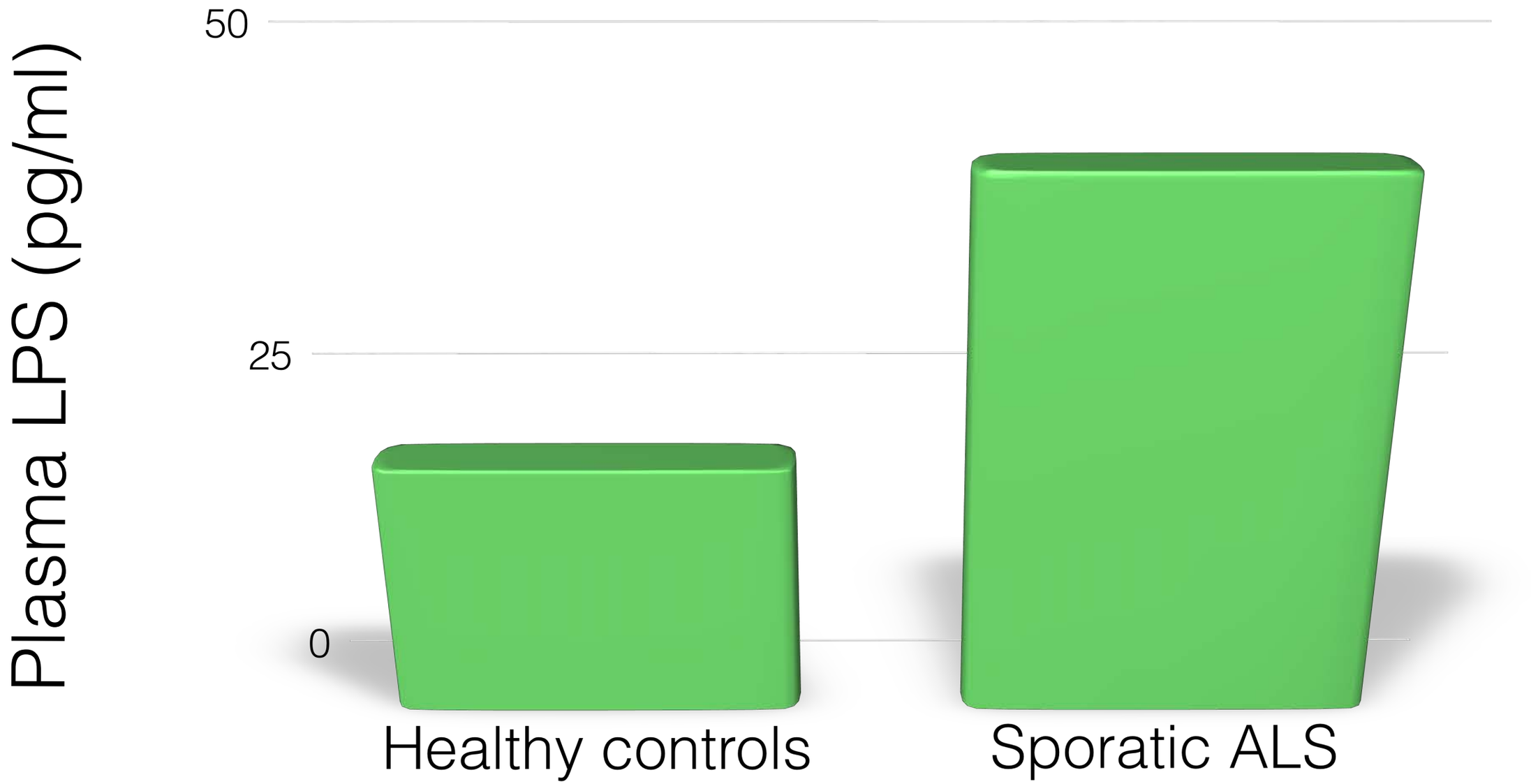

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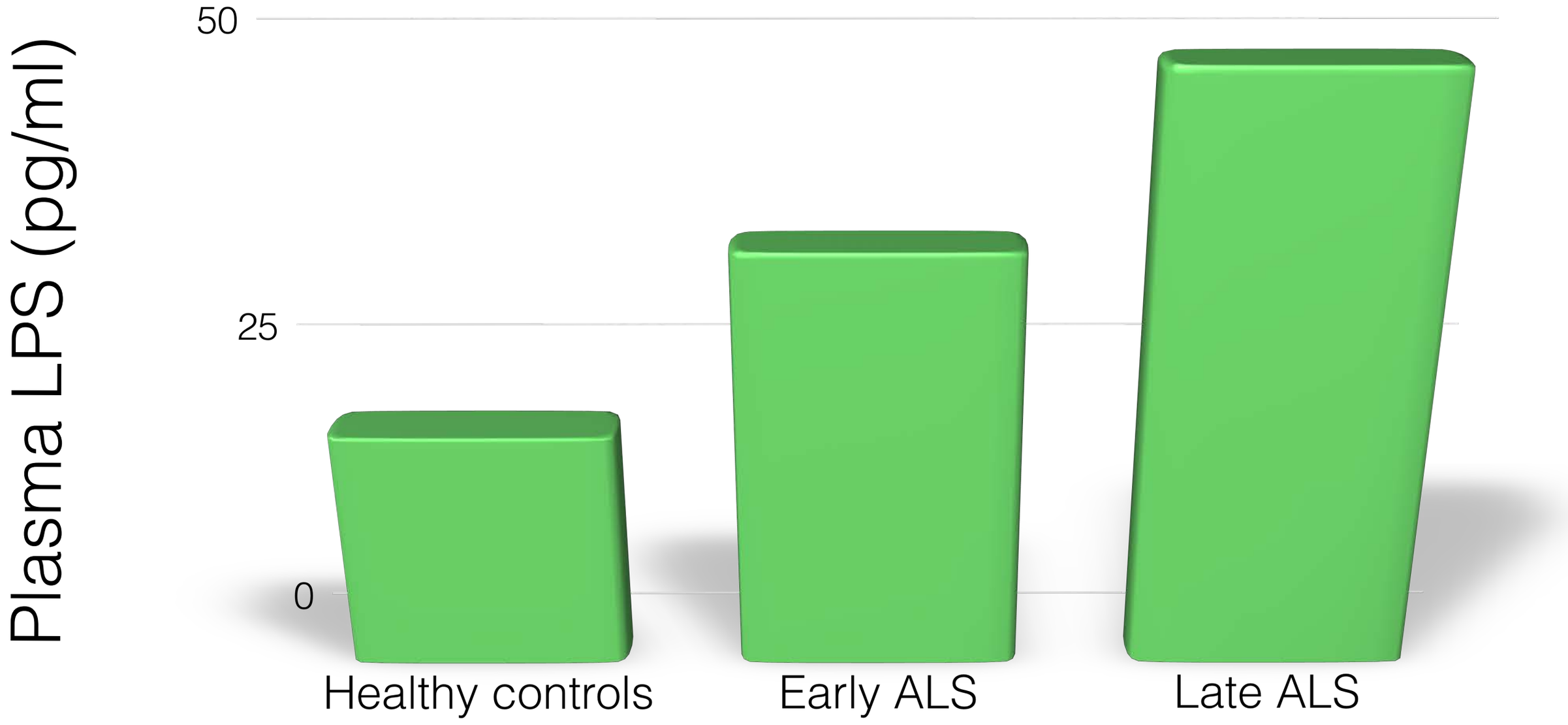

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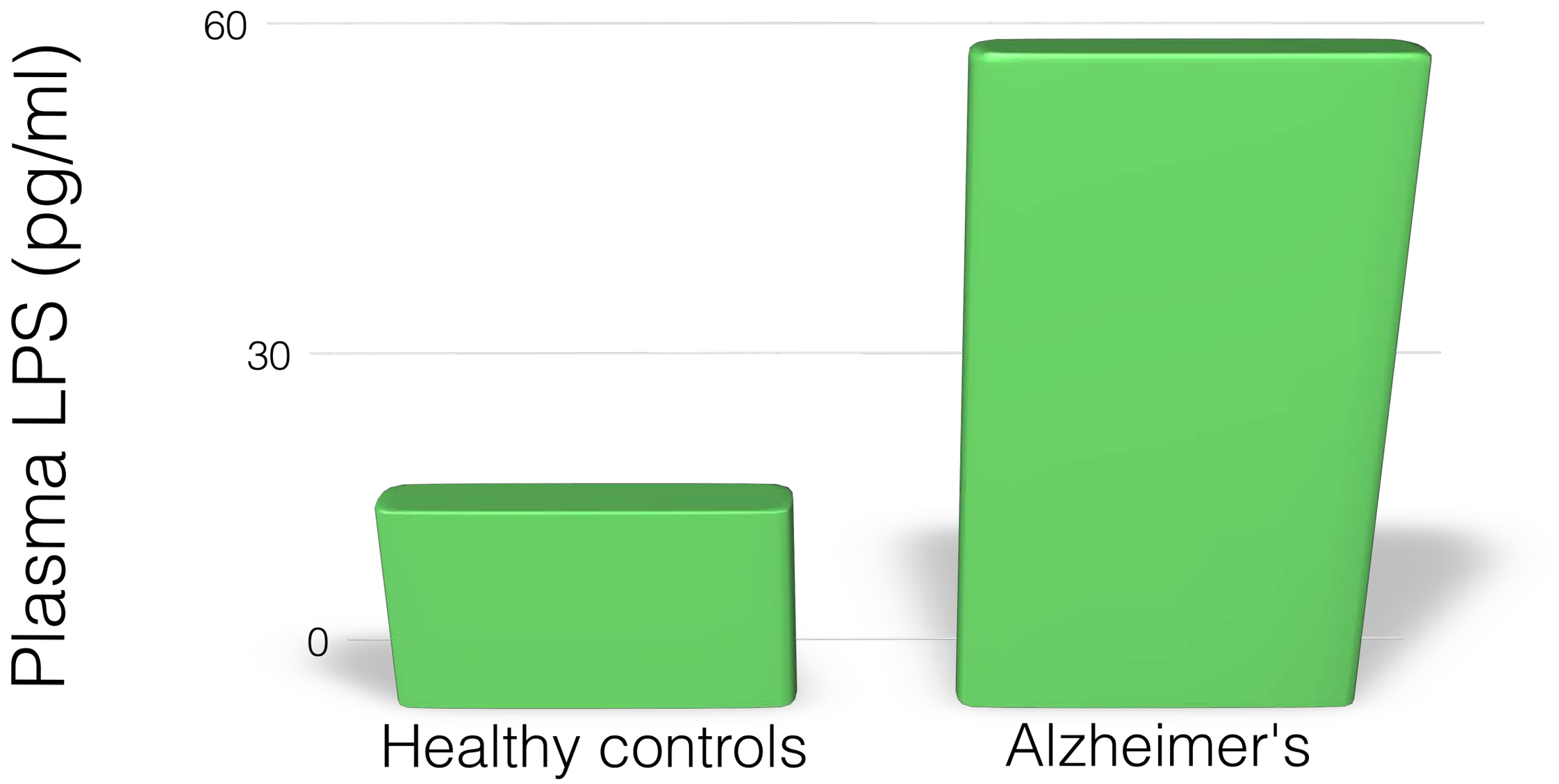
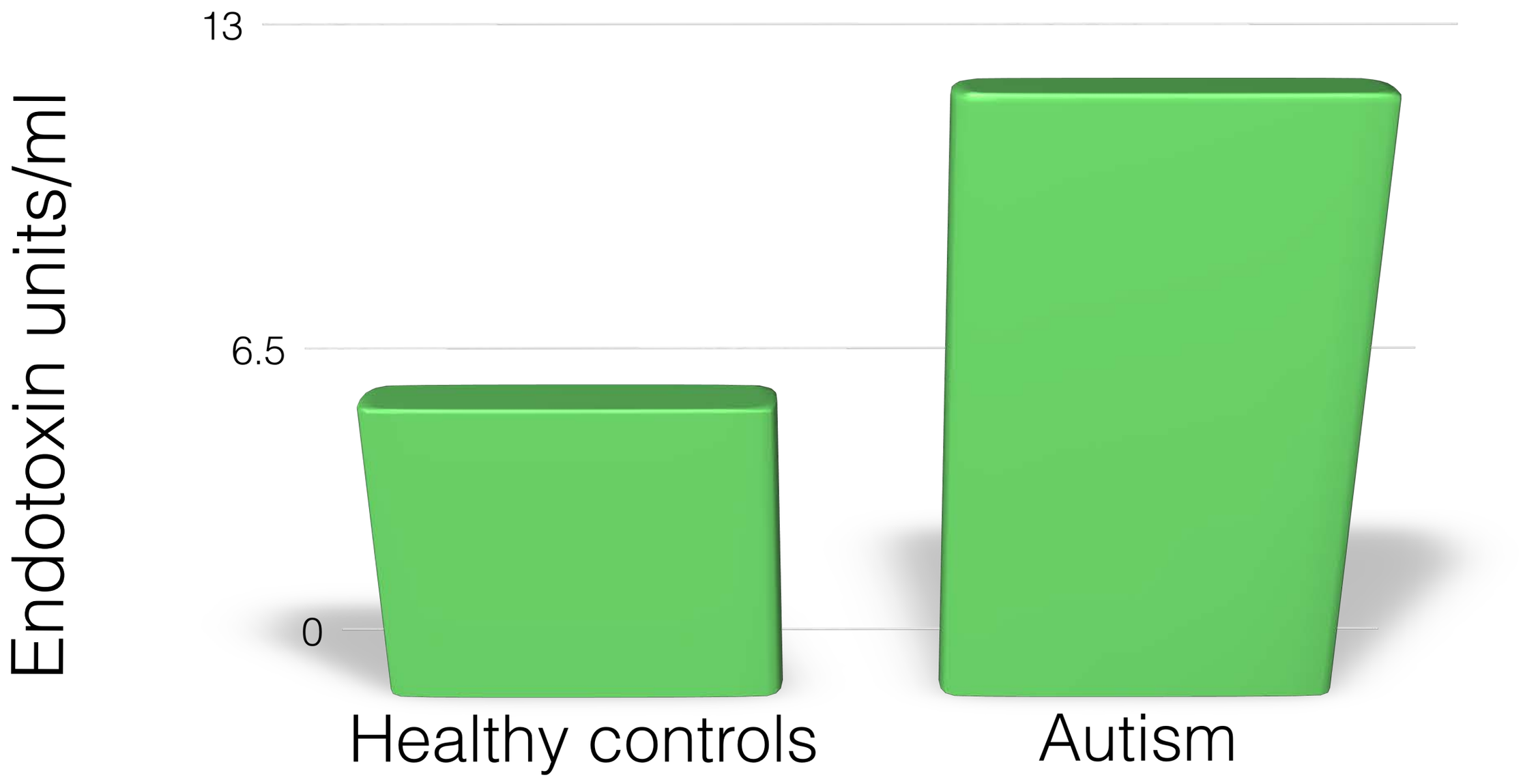


Zhang, R., et al., J. Neuroimmunol. 2009; (206): 121-4,



Emanuele, E., et al., Neuroscience Letters 471 (2010) 162-5

Gut permeability and the microbiome

Systemic IgM-mediated response against LPS suggests bacterial translocation - “leaky gut”

BMC Medicine 2013, 11:200

- Antibiotics
- Method of delivery
- Medications
- Water treatment
- Diet
- Hormone therapy
- GMO

PEER-REVIEWED CONSULTATIONS IN PRIMARY CARE
Consultant

Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

Thu, 08/19/10 - 11:48

Authors:
Ami Kapadia, MD, Daisy Wynn, MD, and Brooke Salzman, MD

Introduction

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have become one of the most commonly prescribed classes of medications in the world. In 2007, PPI sales in the United States were in excess of $11 billion.[1] Esomeprazole and lansoprazole both ranked among the top five drugs sold in the United States in 2007.[1]

Overall, with their high safety profile and demonstrated efficacy, PPIs represent a major advance in the treatment of acid-related disorders ranging from peptic ulcer disease to erosive esophagitis. However, it has been shown that PPIs are often misused and overused, which may have significant implications.[2-7] With the widespread and frequent long-term use of PPIs, several adverse effects have come to light that may call for more selective prescribing practices, particularly in older adults who may be more vulnerable and likely to suffer the consequences of such adverse effects. With an estimated 8% of males and 15% of females age 65 years and older experiencing reflux and potentially using acid-suppressive therapy,[8] understanding the risks for potential adverse effects associated with PPIs is critical in this population.

In this article, we review the current data on selected negative outcomes that may result from PPI use. Specifically, increasing evidence demonstrates that PPI therapy may be associated with the development of *Clostridium difficile* infections, hip fractures, community-acquired pneumonia, vitamin B_{12} deficiency, and possibly immunoglobulin E–mediated allergic reactions. The implications of such adverse outcomes, along with the evidence of the inappropriate use of PPIs, underscore the need for more judicious use of this class of medications.

Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

Specifically, increasing evidence demonstrates that PPI therapy may be associated with the development of:

- *Clostridium difficile* infections
- hip fractures
- community acquired pneumonia
- vitamin B12 deficiency
- allergic reactions

Consultant 360. November, 2015

Potential Adverse Effects of Proton Pump Inhibitors in the Elderly

The etiology of these side effects, particularly diarrhea, may be related to alterations in gut flora caused by acid suppression.

Consultant 360. November, 2015

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

PLOS | ONE

RESEARCH ARTICLE

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Nigam H. Shah[1☯]*, Paea LePendu[1☯], Anna Bauer-Mehren[1], Yohannes T. Ghebremariam[2], Srinivasan V. Iyer[1], Jake Marcus[3], Kevin T. Nead[4], John P. Cooke[2], Nicholas J. Leeper[4]

1 Stanford Center for Biomedical Informatics Research, Stanford University, Stanford, CA, United States of America, **2** Department of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX, United States of America, **3** Practice Fusion, Inc., San Francisco, CA, United States of America, **4** Divisions of Cardiovascular Medicine and Vascular Surgery, Stanford University, Stanford, CA, United States of America

☯ These authors contributed equally to this work.
* nigam@stanford.edu

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Data Availability Statement: The data in consideration are electronic medical records of patients at Stanford university, and medical records of a subset of patients at Practice Fusion. Current patient privacy rules do not allow sharing of electronic medical records without an explicit IRB review. The authors can make access to de-identified data available after appropriate approvals. Contact: Nigam Shah, nigam@stanford.edu.

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Abstract

Background and Aims

Proton pump inhibitors (PPIs) have been associated with adverse clinical outcomes amongst clopidogrel users after an acute coronary syndrome. Recent pre-clinical results suggest that this risk might extend to subjects without any prior history of cardiovascular disease. We explore this potential risk in the general population via data-mining approaches.

Methods

Using a novel approach for mining clinical data for pharmacovigilance, we queried over 16 million clinical documents on 2.9 million individuals to examine whether PPI usage was associated with cardiovascular risk in the general population.

Results

In multiple data sources, we found gastroesophageal reflux disease (GERD) patients exposed to PPIs to have a 1.16 fold increased association (95% CI 1.09–1.24) with myocardial infarction (MI). Survival analysis in a prospective cohort found a two-fold (HR = 2.00; 95% CI 1.07–3.78; P = 0.031) increase in association with cardiovascular mortality. We found that this association exists regardless of clopidogrel use. We also found that H_2 blockers, an alternate treatment for GERD, were not associated with increased cardiovascular risk; had they been in place, such pharmacovigilance algorithms could have flagged this risk as early as the year 2000.

Conclusions

Consistent with our pre-clinical findings that PPIs may adversely impact vascular function, our data-mining study supports the association of PPI exposure with risk for MI in the

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Review of 16 million clinical documents of 2.9 million individuals

PLOS ONE, June 10, 2015

Stanford University

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Association with PPIs:

- Myocardial infarction - increased 16%
- Death from myocardial infarction - risk is doubled

PLOS ONE, June 10, 2015

Stanford University

Association of Proton Pump Inhibitors With Risk of Dementia

Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.

OBJECTIVE To examine the association between the use of PPIs and the risk of incident dementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.

MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of incident dementia coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.

RESULTS A total of 73 679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2950; mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70 729; mean [SD] age, 83.0 [5.6] years; 73.6% female) (hazard ratio, 1.44 [95% CI, 1.36-1.52]; $P < .001$).

CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are needed to examine this connection in more detail.

Editorial page 379

Supplemental content at jamaneurology.com

JAMA Neurol. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791
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Author Affiliations: German Center for Neurodegenerative Diseases, Bonn, Germany (Gomm, von Holt, Thomé, Maier, Fink, Doblhammer, Haenisch); Federal Institute for Drugs and Medical Devices, Bonn, Germany (Broich); Department of Psychiatry, University of Bonn, Bonn, Germany (Maier); Rostock Center for the Study of Demographic Change, Rostock, Germany (Fink, Doblhammer); Max-Planck-Institute for Demographic Research, Rostock, Germany (Doblhammer); Institute for Sociology and Demography, University of Rostock, Rostock, Germany (Doblhammer).

Corresponding Author: Britta Haenisch, PhD, German Center for Neurodegenerative Diseases, c/o Federal Institute for Drugs and Medical Devices, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany (britta.haenisch@dzne.de).

Association of Proton Pump Inhibitors With Risk of Dementia

- 73,679 dementia free adults
- aged ≥ 75 years
- followed for 5.4 - 5.6 years

JAMA Neurology. February 15, 2016

Association of Proton Pump Inhibitors With Risk of Dementia

Risk of dementia in regular users of PPI drugs was increased by 44%.

JAMA Neurology. February 15, 2016

Association of Proton Pump Inhibitors With Risk of Dementia

"Thus, the avoidance of PPI medication may contribute to the prevention of dementia."

JAMA Neurology. February 15, 2016

Probiotic foods

- kimchi
- sauerkraut
- yogurt
- kefir
- kombucha

Prebiotic foods

- jicama
- dandelion greens
- garlic
- chickory root
- Jerusalem artichoke

Probiotic foods and supplements

Prebiotic foods and supplements

Lower carbohydrates

More healthy fat

Magnesium

Aerobic exercise

DHA

Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Utilize innovative laboratory studies to both recognize as well as remediate gut permeability issues
- Apply the knowledge gained in this presentation to cultivate lifestyle recommendations for patients/ clients to change their brain's health destiny