

Nexus between nutrition, microbiome and cardiovascular health

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IN DER HELMHOLTZ-GEMEINSCHAFT

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No disclosures

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Outline

- Conceptual facts
- High salt intake and the microbiome
- SCFA in cardiovascular and autoimmune disease
- Perspective

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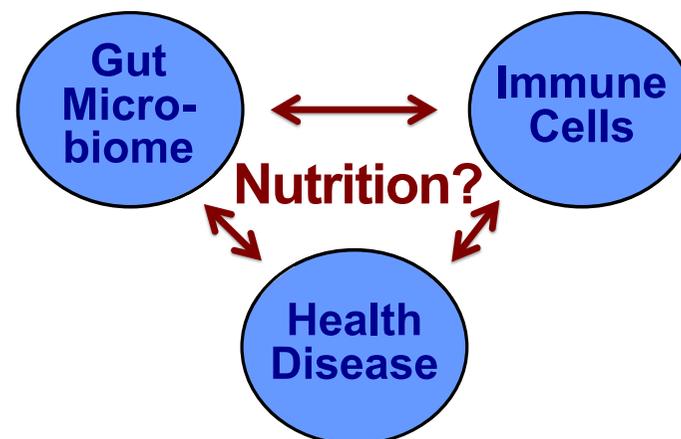
Why do we have 1.5 kg gut bacteria?



<http://io9.gizmodo.com/is-it-really-worth-having-your-gut-bacteria-tested-1507503526>

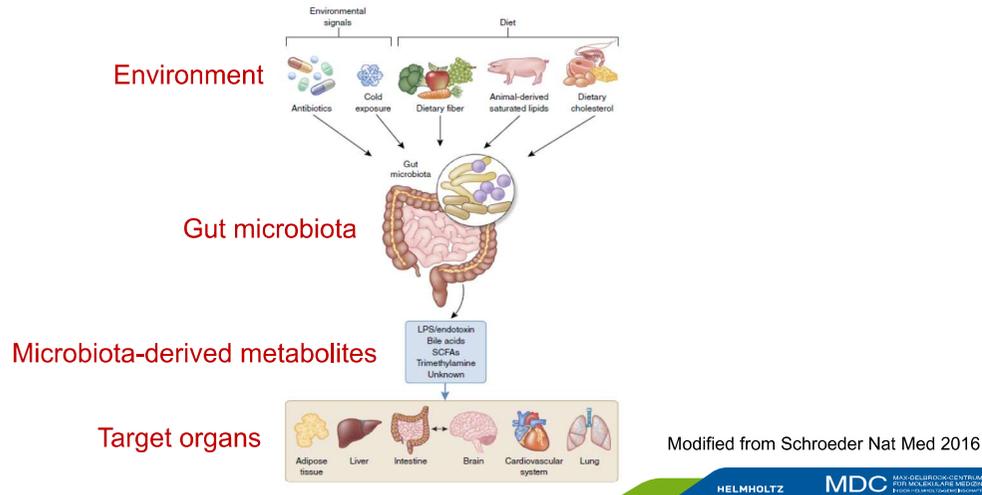
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Microbiome - host immune interaction

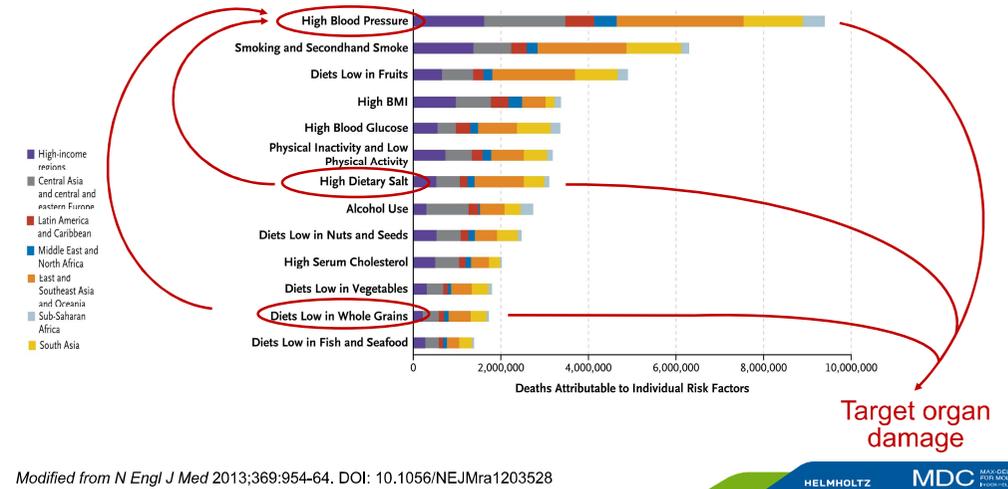


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Host-Microbiome Interaction



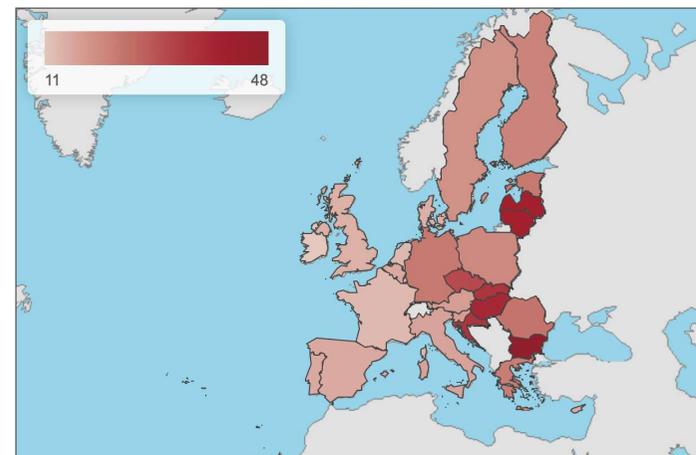
Hypertension – the leading global risk factor



We eat too much salt...

- ...and everyone knows it, but...
- Our guidelines: 1.5-2.4 g Na⁺ or 4-6 g salt per day
- Pizza: 5-10 g salt
- PURE Study: only 4% of adults on goal¹
- High salt intake contributes to cardiovascular morbidity and mortality
- Worldwide 1.65 million deaths in 2010²

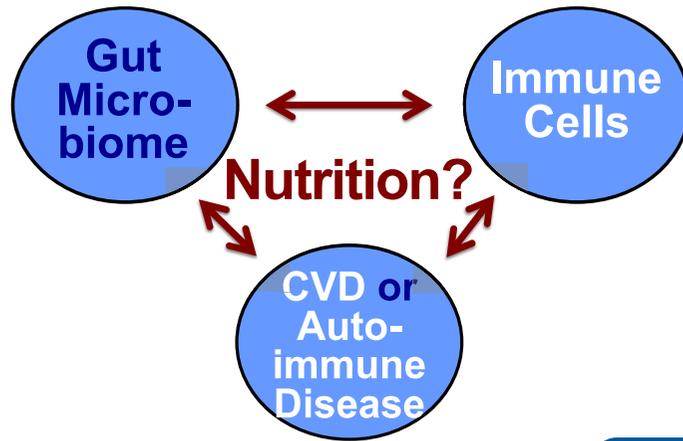
Mortality map: death/100 000 attributable to diet low in fiber



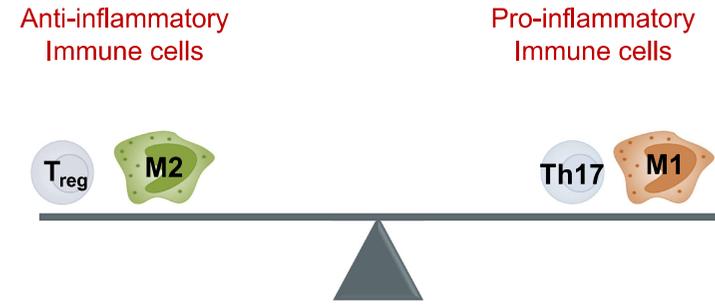
Country	Rate
Belgium	15
Bulgaria	48
Czechia	31
Denmark	14
Germany	23
Estonia	23
Ireland	11
Greece	22
Spain	15
France	13
Croatia	35
Italy	16
Cyprus	15
Latvia	40
Lithuania	40
Luxembourg	13
Hungary	38
Malta	20
Netherlands	13
Austria	17
Poland	20
Portugal	15
Romania	24
Slovenia	17
Slovakia	35
Finland	21
Sweden	19
United Kingdom	14

¹ Mente and O'Donnell et al. NEJM 2014 ² Mozaffarian et al. NEJM 2014

Microbiome - host immune interaction



Immune cell homeostasis



T cells in health and (cardiovascular) disease

- Th1:** cell-mediated immunity; bacterial and parasitic infections
- Th2:** humoral immunity; allergic immune response; anti-helminth immune response
- Th17:** increased autoimmunity; anti-fungal immune response
- Treg:** decrease autoimmune inflammation

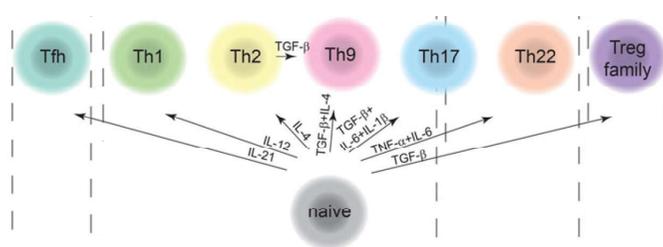


Figure from Eyerich S Eur. J. Immunol. 2014

T cells in health and (cardiovascular) disease

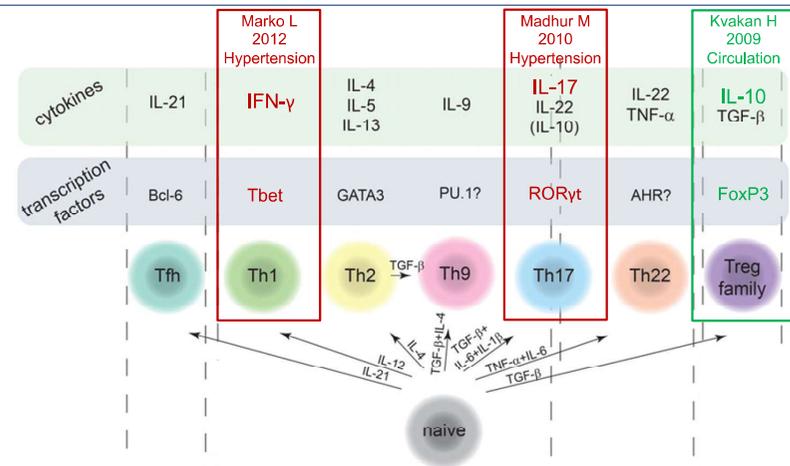
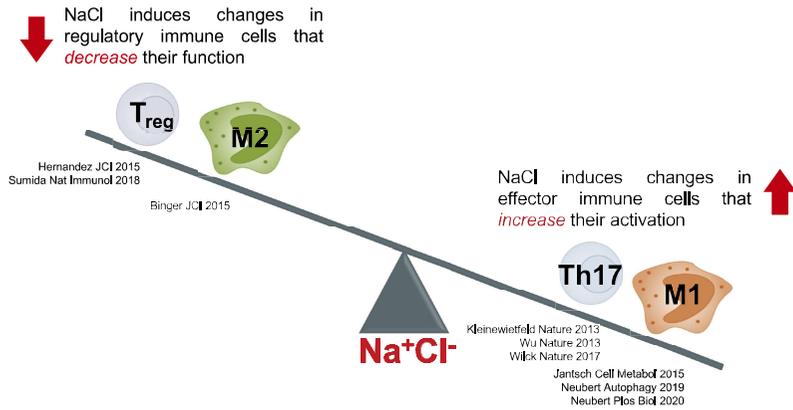
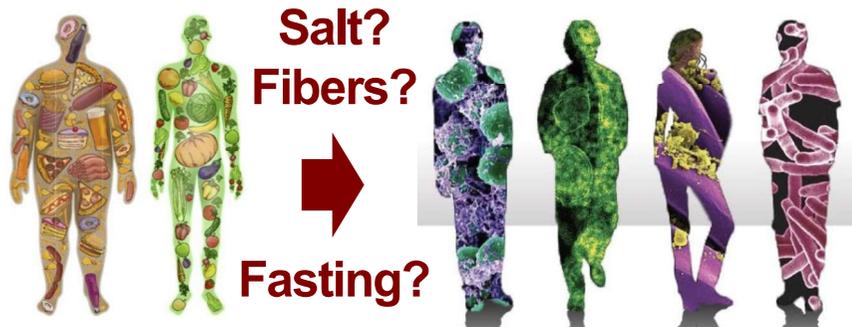


Figure from Eyerich S Eur. J. Immunol. 2014

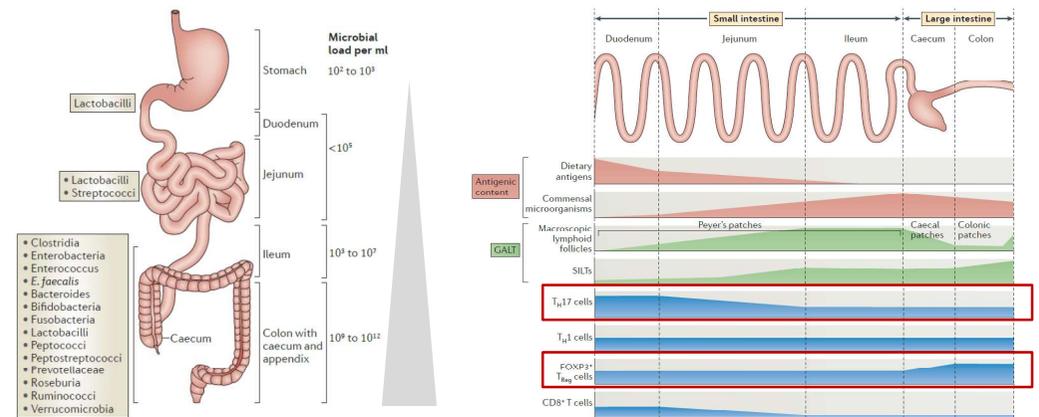
High salt and immune cell imbalance



What we eat affects our microbes

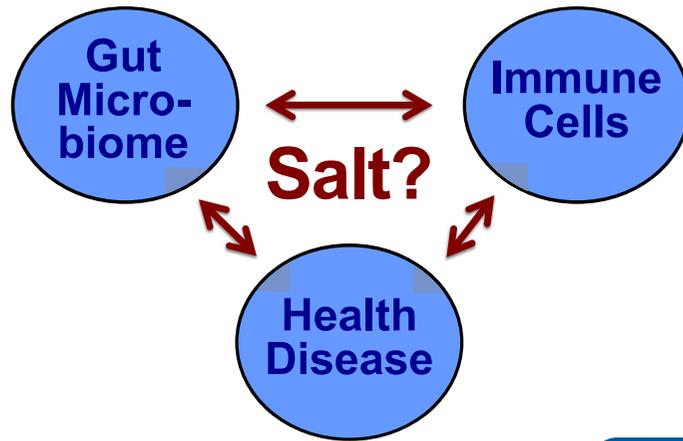


The intestinal microbiome

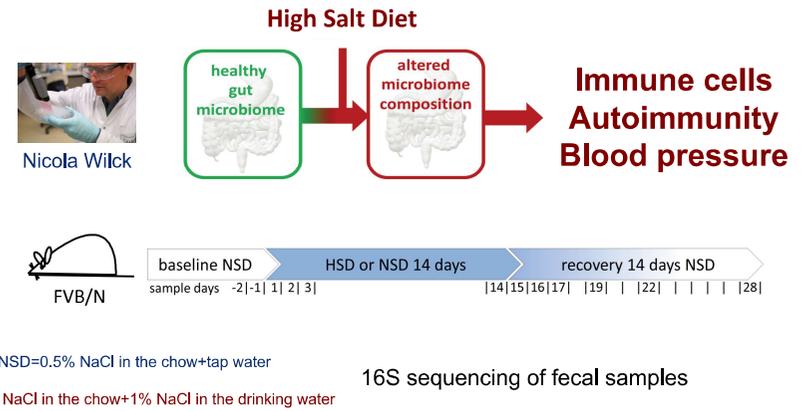


Modified from Mowat Nature Reviews Immunology 2014

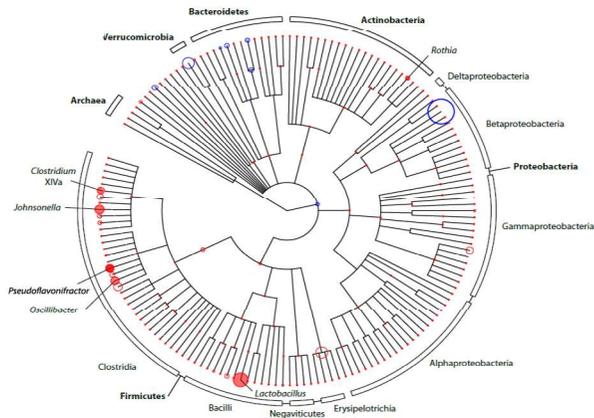
Microbiome - host immune interaction



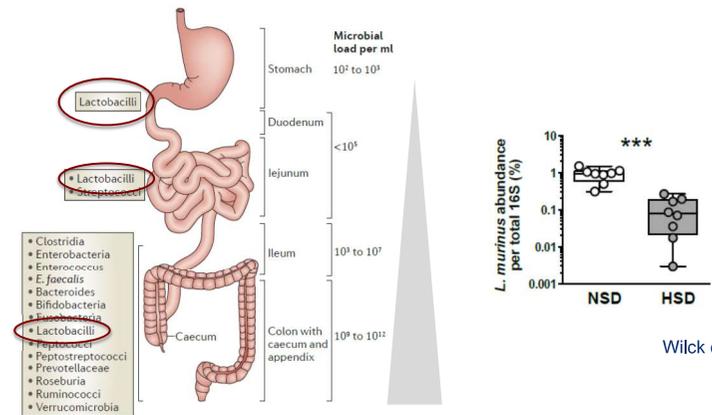
High salt intake and the gut microbiome



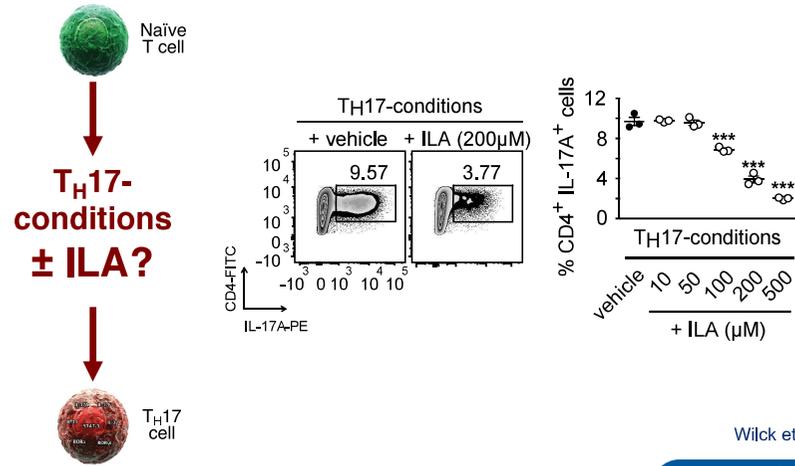
High salt induces fine-scale alterations in gut microbiome composition



Role of high salt on *Lactobacilli*

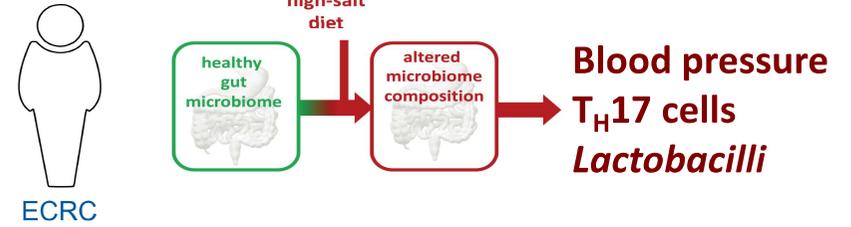


ILA acts as endogenous T_H17 inhibitor



Wick et al. Nature 2017

Clinical Trial (NCT02509962)



Healthy male subjects

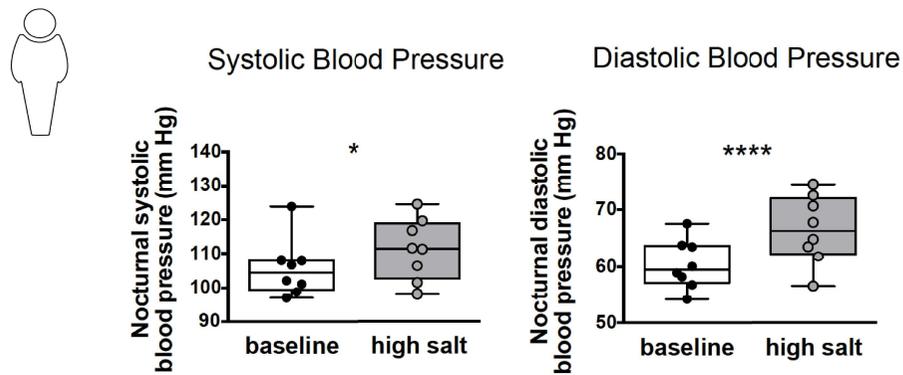
6 g NaCl/day (Slow Sodium Tablets) for 14 days

Nocturnal blood pressure monitoring

PBMC isolation: flow cytometry for T_H17

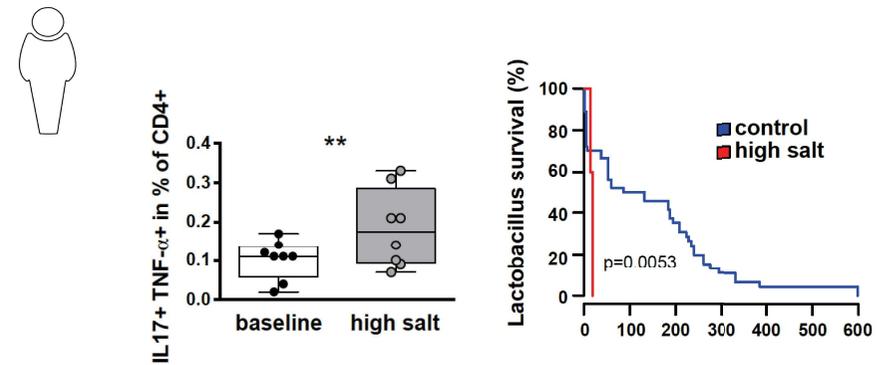
Fecal samples: metagenomics for microbiome composition

High salt and salt-sensitive hypertension



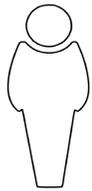
Wick et al. Nature 2017

High salt affects T_H17 cells and gut *Lactobacillus*



Wick et al. Nature 2017

Lactobacillus blunts hypertension



Placebo vs.

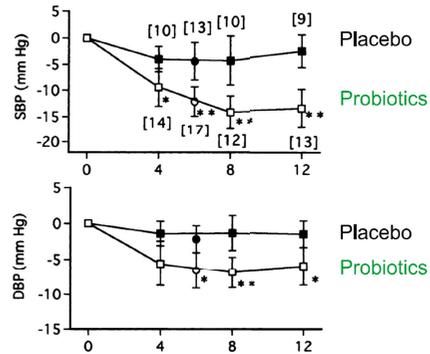
Probiotics
Sour milk containing
L. helveticus 7x10¹⁰
S. cerevisiae 2.5x10⁸

Hata et al. Am J Clin Nutr 1996

Clinical Trial
(NCT03906578)



Randomized placebo-controlled double-blind
clinical study in stage I hypertensive subjects



Link between high salt and SCFA

Clinical Trial

Modest Sodium Reduction Increases Circulating Short-Chain Fatty Acids in Untreated Hypertensives A Randomized, Double-Blind, Placebo-Controlled Trial

Li Chen, Feng J. He, Yanbin Dong, Ying Huang, Changqiong Wang, Gregory A. Harshfield, Haidong Zhu

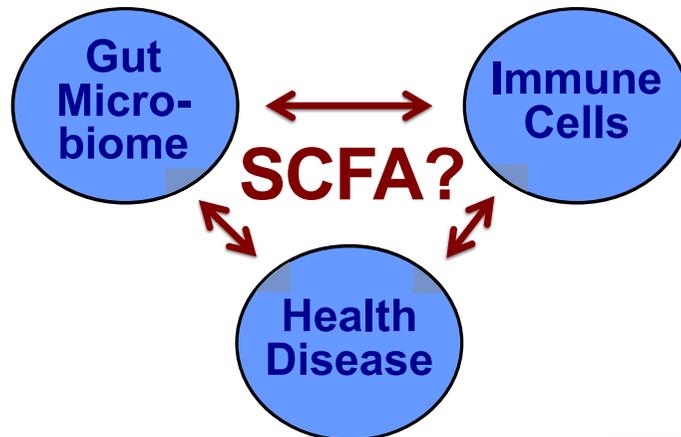
Abstract—High-sodium diet may modulate the gut microbiome. Given the circulating short-chain fatty acids (SCFAs) are microbial in origin, we tested the hypothesis that the modest sodium reduction would alter circulating SCFA concentrations among untreated hypertensives, and the changes would be associated with reduced blood pressure and improved cardiovascular phenotypes. A total of 145 participants (42% blacks, 19% Asian, and 34% females) were included from a randomized, double-blind, placebo-controlled cross-over trial of sodium reduction with slow sodium or placebo tablets, each for 6 weeks. Targeted circulating SCFA profiling was performed in paired serum samples, which were collected at the end of each period, so as all outcome measures. Sodium reduction increased all 8 SCFAs, among which the increases in 2-methylbutyrate, butyrate, hexanoate, isobutyrate, and valerate were statistically significant ($P < 0.05$). Also, increased SCFAs were associated with decreased blood pressure and improved arterial compliance. There were significant sex differences of SCFAs in response to sodium reduction ($P < 0.05$). When stratified by sex, the increases in butyrate, hexanoate, isobutyrate, isovalerate, and valerate were significant in females only ($P < 0.05$), not in males ($P > 0.05$). In females, changes in isobutyrate, isovalerate, and 2-methylbutyrate were inversely associated with reduced blood pressures ($P < 0.05$). Increased valerate was associated with decreased carotid-femoral pulse wave velocity ($P = 0.040$). Our results show that dietary sodium reduction increases circulating SCFAs, supporting that dietary sodium may influence the gut microbiome in humans. There is a sex difference in SCFA response to sodium reduction. Moreover, increased SCFAs are associated with decreased blood pressures and improved arterial compliance.

Registration—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT00152074. (*Hypertension*. 2020;76:73-79. DOI: 10.1161/HYPERTENSIONAHA.120.14800.) • Data Supplement

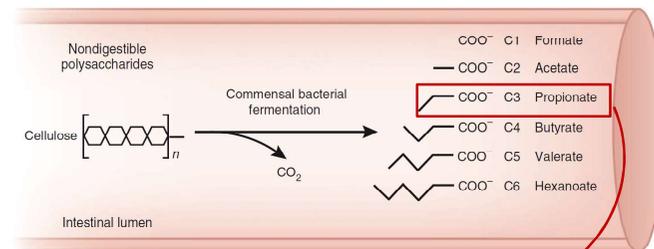
Key Words: blood pressure ■ short-chain fatty acids ■ hypertension ■ phenotype ■ sodium

Chen et al. Hypertension 2020

Microbiome - host immune interaction



Short chain fatty acids (SCFA)

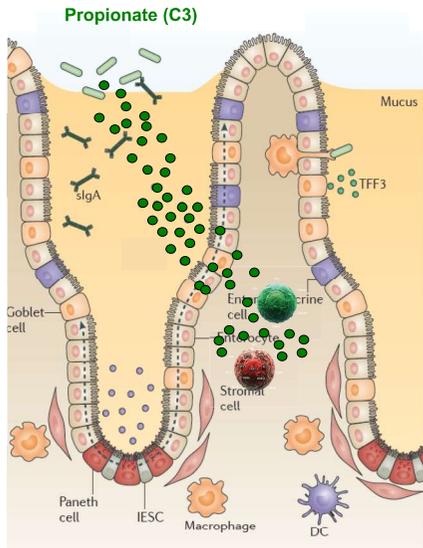


Colonic lumen: 50 - 100 mM Blood: 1 - 400 μM

SCFA (butyrate, propionate)

- induce the differentiation of colonic regulatory T cells (Treg)
- affect the Treg/Th17 balance

Cummings JH et al. *Gut* 1987; Arpaia N. *Nature* 2013; Furasawa Y *Nature* 2013; Smith PM *Science* 2013; Park J *Mucosal Immunology* 2014

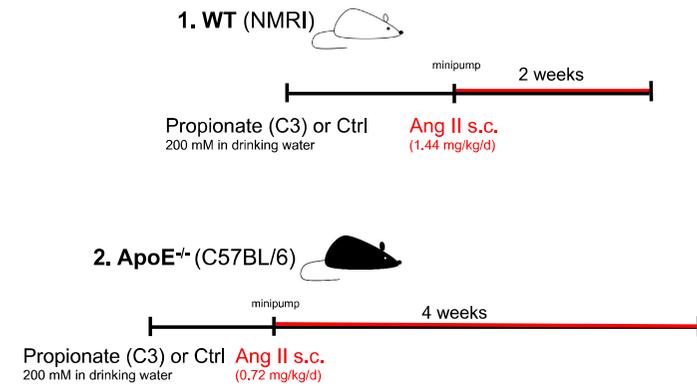


Does the direct application of SCFA (propionate) ameliorate vascular and cardiac damage

?

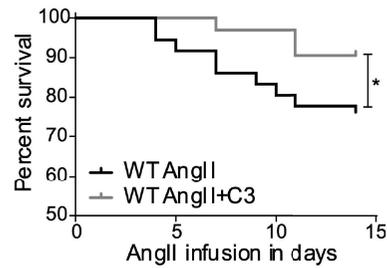
Modified from Peterson Nature Review Immunology 2014

Role of propionate on vascular and cardiac damage

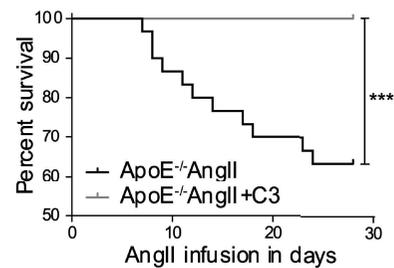


SCFA treatment improves survival

Hypertension-induced organ damage

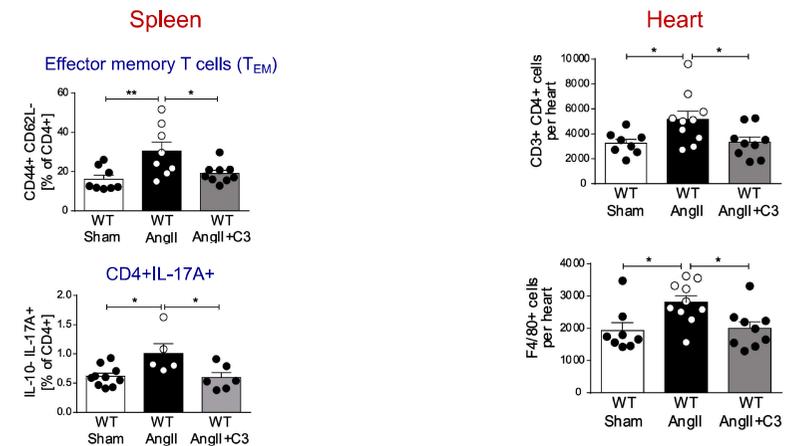


Hypertension-induced atherosclerosis



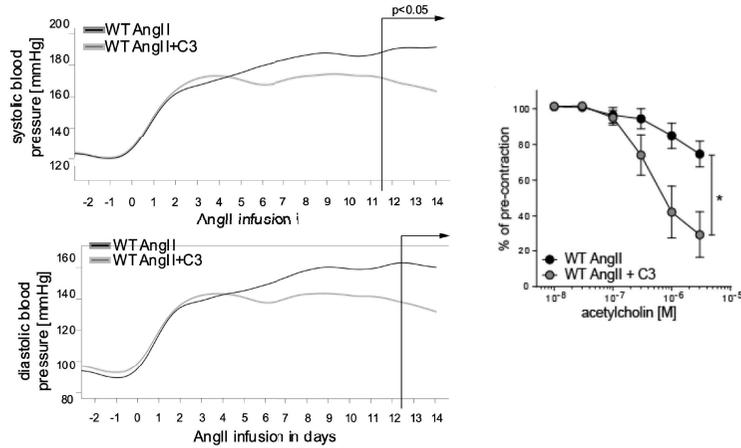
Bartolomaeus et al. Circulation 2018

SCFA treatment reduces inflammation



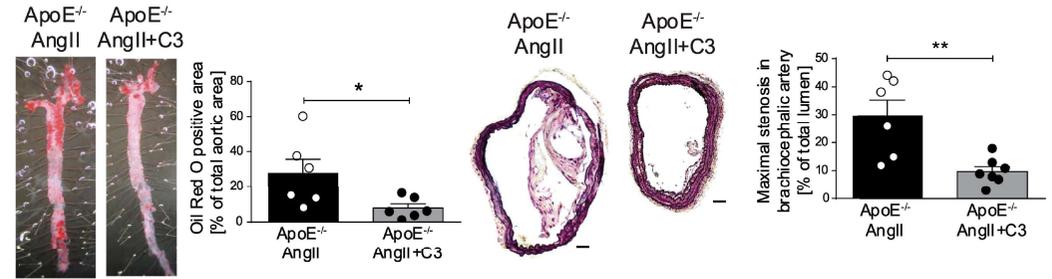
Bartolomaeus et al. Circulation 2018

SCFA improves blood pressure and vascular function



Bartolomaeus et al. Circulation 2018

SCFA treatment improves atherosclerotic lesions



Bartolomaeus et al. Circulation 2018

SCFA treatment improves autoimmunity



Immunity
Article

Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine

Aiden Haghikia,^{1,10,*} Stefanie Jörg,^{2,10} Alexander Duscha,¹ Johannes Berg,¹ Arndt Manzel,² Anne Waschbisch,² Anna Hammer,² De-Hyung Lee,² Caroline May,² Nicola Wick,² Andras Balogh,² Annika I. Ostermann,² Nils Helge Schebb,² Denis A. Akkad,² Diana A. Grohme,² Markus Kleinewietfeld,² Stefan Kempa,² Jan Thöne,² Seray Demir,¹ Dominik N. Müller,^{1,10} Ralf Gold,^{1,10} and Ralf A. Linker,^{1,10}

2015 DOI: 10.1016/j.immuni.2015.09.007

Article

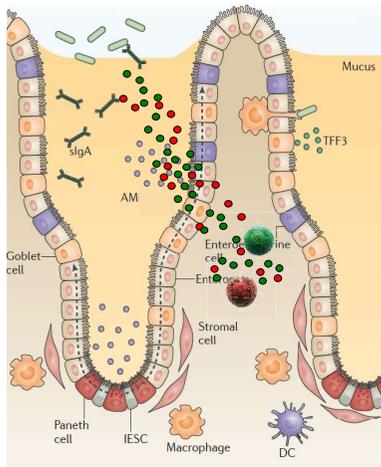
Propionic Acid Shapes the Multiple Sclerosis Disease Course by an Immunomodulatory Mechanism

Alexander Duscha,^{1,10} Barbara Gieseius,^{1,10} Sarah Hirschberg,^{1,10} Nissan Yissachar,^{2,10} Gabriele I. Stangl,¹ Eva Eilers,^{5,6} Verian Bader,² Stefanie Haase,² Johannes Keister,¹ Christina David,¹ Ruth Schneider,¹ Riccardo Troisi,¹ Daniel Zent,¹ Tobias Hegelmaier,¹ Nikolaos Dokkalis,¹ Sara Genesio,² Sara Del Mare-Roumani,² Sivan Andriou,² Ori Staszewski,^{8,9} Gereon Poschmann,^{10,11} Kai Stühler,^{10,11} Frank Hirche,² Andras Balogh,¹⁰ Stefan Kempa,¹⁰ Pascal Träger,¹⁴ Mario M. Zalus,¹⁴ Jacob Bak Horn,¹⁴ Megan G. Maasia,¹⁴ Henrik Bjorn Nielsen,¹⁴ Andreas Fassaner,¹⁴ Carsten Lukas,¹⁴ Sören G. Galetzmann,⁹ Markus Scheib,² Horst Przuntek,² Marco Prinz,^{15,16} Sofia K. Forslund,^{15,16} Konstanze F. Winkhofer,¹ Dominik N. Müller,^{1,10} Ralf A. Linker,^{1,10} Ralf Gold,^{1,10} and Aiden Haghikia,^{1,10,*}

2020 DOI: 10.1016/j.cell.2020.02.035

What we eat affects our microbes and our ecosystems





Can we target the gut
to treat
(cardio)vascular disease

?

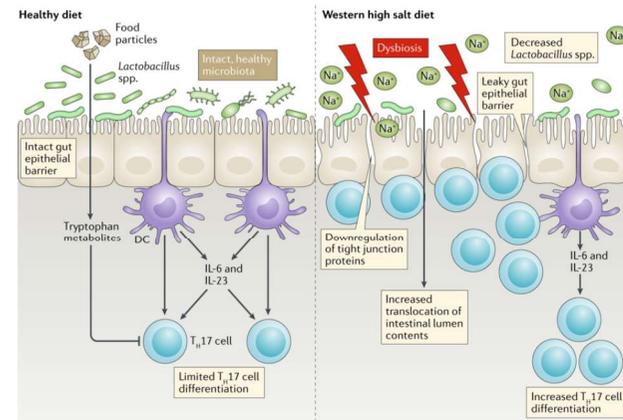
● Disease-preventing metabolites ● Disease-promoting metabolites

Adapted from Peterson Nature Review Immunology 2014

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PROTEINOMIK UND SYSTEMBIOMEDIZIN

Summary



FASTING
might be good
for your dysbiosis

Muller et al. Nature Review Immunology 2019

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