swiss**milk**

Darmgesundheit Symposium für Ernährungsfachleute



Medizinische Universität Graz



Das Gehirn unter dem Einfluss des Darmmikrobioms

Peter Holzer



Forschungseinheit für Translationale Neurogastroenterologie Institut für Experimentelle und Klinische Pharmakologie

Gut microbiota – gut – brain axis





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Gut microbiota and neuropsychiatric disorders

	Cognitive impairment in hepatic encephalopathy
Cognitive impairment in diabetes	
	Alzheimer's disease
Neuroinflammation and ageing-rela	ted synaptic dysfunction
	Parkinson's disease
Cerebral cavernous malformations	(stroke, seizures)
	Autism spectrum disorders
Multiple sclerosis	
	Anxiety disorders
Depression	
	Stress vulnerability
Chronic fatigue syndrome	
	Irritable bowel syndrome



Causality in gut microbiota-brain interaction





Nat Rev Neurosci 2012;13:701-712

John F. Cryan^{1,2} and Timothy G. Dinan^{1,3}

Behavioural alterations in germ-free mice





Zheng P et al. Mol Psychiatry 2016;21:786-796

Dysfunctional blood-brain barrier in germ-free mice



The blood-brain barrier of germ-free (GF) mice is permanently impaired as shown by functional studies and reduced expression of tight junction proteins

Neurochemical alterations Microglial alterations Ultrastructural alterations



Diaz Heijtz R et al. *Proc Natl Acad Sci USA* 2011,108:3047-3052 Braniste V et al. *Sci Transl Med* 2014;6:263ra158 Erny D et al. *Nat Neurosci* 2015;18:965-977

Host microbiota constantly control maturation and function of microglia in the CNS

Daniel Erny^{1,12}, Anna Lena Hrabě de Angelis^{1,12}, Diego Jaitin², Peter Wieghofer^{1,3}, Ori Staszewski¹, Eyal David², Hadas Keren-Shaul², Tanel Mahlakoiv⁴, Kristin Jakobshagen⁵, Thorsten Buch⁶, Vera Schwierzeck⁷, Olaf Utermöhlen⁵, Eunyoung Chun⁸, Wendy S Garrett⁸, Kathy D McCoy⁹, Andreas Diefenbach⁷, Peter Staeheli⁴, Bärbel Stecher¹⁰, Ido Amit² & Marco Prinz^{1,11}



Erny D et al. *Nat Neurosci* 2015;18:965-977 Mosher KI, Wyss-Coray T. *Nat Neurosci* 2015;18:930-931



Obesity through microbiota transplantation

Transfer of obesity from humans to mice by way of faecal transplantation



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Ridaura VK et al. *Science* 2013;341:1241214-1-1241214-10 Walker AW, Parkhill J. *Science* 2013;341:1069-1070

Depression through microbiota transplantation

Depression is transferred from patients to mice via transplantation of faecal microbiota





Zheng P et al. Mol Psychiatry 2016;21:786-796

Anxiety through microbiota transplantation

Anxiety is transferred from mouse to mouse via transplantation of faecal microbiota





Bercik P et al. Gastroenterology 2011;141:599-609

Alterations in brain function of germ-free mice

Changes observed

Hyperactivity

Reduced anxiety

Reduced depression-like behaviour

Cognitive impairment

Leaky blood-brain barrier

Dysfunctional microglia

Ultrastructure of synapses

Neurotransmitter expression

Neurotrophin and neuropeptide expression

Exaggerated stress response





Antibiotic-induced dysbiosis





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Fröhlich et al. Brain Behav Immun 2016;56:140-155

Antibiotic-induced dysbiosis impairs cognition and reduces anxiety



NORTNovel object recognition testEPMElevated plus maze test

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Fröhlich et al. Brain Behav Immun 2016;56:140-155

Antibiotic treatment (10 d)

- Bacitracin
- Ampicillin
- Vancomycin
- Meropenem
- Neomycin

Antibiotic-induced changes in colonic metabolites

Antibiotic treatment (10 d)

- Bacitracin
- Ampicillin
- Vancomycin
- Meropenem
- Neomycin

Scores plot of the principal component analysis with 21 identified colonic metabolites analyzed by ¹H NMR







Fröhlich et al. Brain Behav Immun 2016;56:140-155

Short chain fatty acids as microbial hormones





Bindels LB et al. Trends Pharmacol Sci 2013;34:226-232

Peptide YY: an antidepressant hormone



OF Open field test FST Forced swim test

Knockout of peptide YY, the release of which is increased by SCFAs, causes depression



Painsipp E, Herzog H, Sperk G, Holzer P. Br J Pharmacol 2011;163:1302-1314

Gut dysbiosis and brain NPY system

Antibiotic treatment (10 d)

- Bacitracin
- Ampicillin
- Vancomycin
- Meropenem
- Neomycin







NPYSR

- VEH

AB





Cognitive impairment in NPY2R knockout mice





Evelin Painsipp

Painsipp E, Wultsch T, Edelsbrunner ME, Tasan RO, Singewald N, Herzog H, Holzer P. *Genes Brain Behav* 2008;7:532-542



Disturbed development of gut microbiota causes longterm visceral hyperalgesia



Treatment of newborn rats with vancomycin for 9 days causes pain hypersensitivty in adult animals

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O'Mahony SM et al. Neuroscience 2014; 277:885-901

Alterations in gut – brain communication following antibiotic treatment



Gut dysbiosis

Colonic metabolite profile in mice

Circulating metabolite profile in mice

Disturbed development of gut microbiota in antibiotic-treated infants

Life-long visceral pain hypersensitivity in rats treated with antibiotics as neonates

Reduced anxiety in mice

Cognitive impairment in mice

Neurotrophin and neuropeptide expression





Gut microbiota – gut – brain axis





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Dysfunctional mucosal barrier: immune activation





Immune activation, sickness and depression



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Diet quality impacts on mental health

Public Health Nutrition: page 1 of 9

doi:10.1017/S1368980011001856

Fast-food and commercial baked goods consumption and the risk of depression

Almudena Sánchez-Villegas^{1,2,*}, Estefania Toledo², Jokin de Irala², Miguel Ruiz-Canela², Jorge Pla-Vidal³ and Miguel A Martínez-González² ¹Centre for Health Sciences, Department of Clinical Sciences, University of Las Palmas de Gran Canaria, PO Box 550, CP 35080, Las Palmas de Gran Canaria, Spain: ²Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain: ³Department of Psychiatry and Medical Psychology, Clinic of the University of Navarra, Pamplona, Spain

- Longitudinal study over 6.2 years
- 8964 Spanish participants

Obesity increases the incidence of psychiatric disorders

Simon GE et al. Arch Gen Psychiatry 2006;63:824-830

OPEN access Freely available online

PLos one

A Prospective Study of Diet Quality and Mental Health in Adolescents

Felice N. Jacka^{1,2}*, Peter J. Kremer³, Michael Berk^{1,2,4,5}, Andrea M. de Silva-Sanigorski⁶, Marjorie Moodie⁷, Eva R. Leslie³, Julie A. Pasco⁸, Boyd A. Swinburn⁹

1 Barwon Psychiatric Research Unit, Deakin University, Geelong, Australia, 2 Department of Psychiatry, University of Melbourne, Melbourne, Australia, 3 School of Psychology, Deakin University, Geelong, Australia, 4 Orygen Youth Health, University of Melbourne, Melbourne, Australia, 5 Mental Health Research Institute, Melbourne, Australia, 6 Jack Brockhoff Child Health and Wellbeing Program, Melbourne School of Population Health, University of Melbourne, Australia, 7 Deakin Health Economics, Deakin University, Melbourne, Australia, 8 Barwon Epidemiology and Biostatistics Unit, Deakin University, Geelong, Australia, 9 WHO Collaborating Centre for Obesity Prevention, Deakin University, Geelong, Australia

PLoS ONE | www.plosone.org

September 2011 | Volume 6 | Issue 9 | e24805

- Longitudinal study over 2 years
- 3040 Australian adolescents, aged 11 18 years



Diet-induced depression



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Potential effects of probiotics





Hill C et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506–514

Anxiolytic and antidepressant effects of probiotics



Treatment of highly anxious Balb/c mice with Lactobacillus rhamnosus (JB-1) for 4 weeks reduces anxiety, depression-like behaviour and stress response

Subdiaphragmatic vagotomy (Vx) prevents the positive effects of the probiotic



Probiotic rescue from diabetes-related cognitive decline





Davari S et al. Neuroscience 2013;240:287-296

Probiotic alters brain activity in healthy humans



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Collins SM, Bercik P. Intestinal bacteria influence brain activity in healthy humans Nat Rev.Gastroenterol Hepatol 2013;10:326-327

Prebiotics are anxiolytic and antidepressant

p = 0.06

F05*605

Anxiety



Depression-like behaviour



Burokas A et al. Biol Psychiatry 2017;82:472-487



Bidirectional gut-brain communication





Thank you



Research Unit of Translational Neurogastroenterology

