2017 - Auckland
HVN conference

What is our second brain thinking?

The relevance of the MGB axis for health

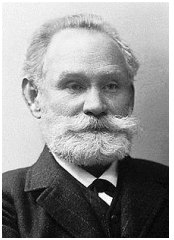
Pierre Déchelotte
INSERM 1073 – IRIB - Nutrition Unit - CHU de Rouen

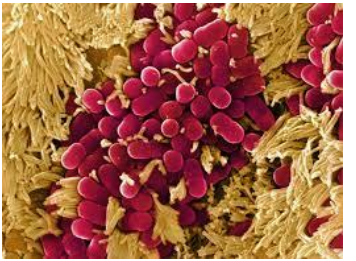
Instituts thématiques
Inserm U 1073
Institut national de la santé et de la recherche médicale
UNIVERSITÉ DE ROUEN
iRiB
CHU Hôpitaux de Rouen

Relevance of the microbiota-gut-brain axis

- **The microbiota-gut-brain axis**
- Weight and eating behaviour
- Digestive diseases : IBD, IBS, Coeliac
- Neuropsychiatric disorders
- Perspectives and challenges

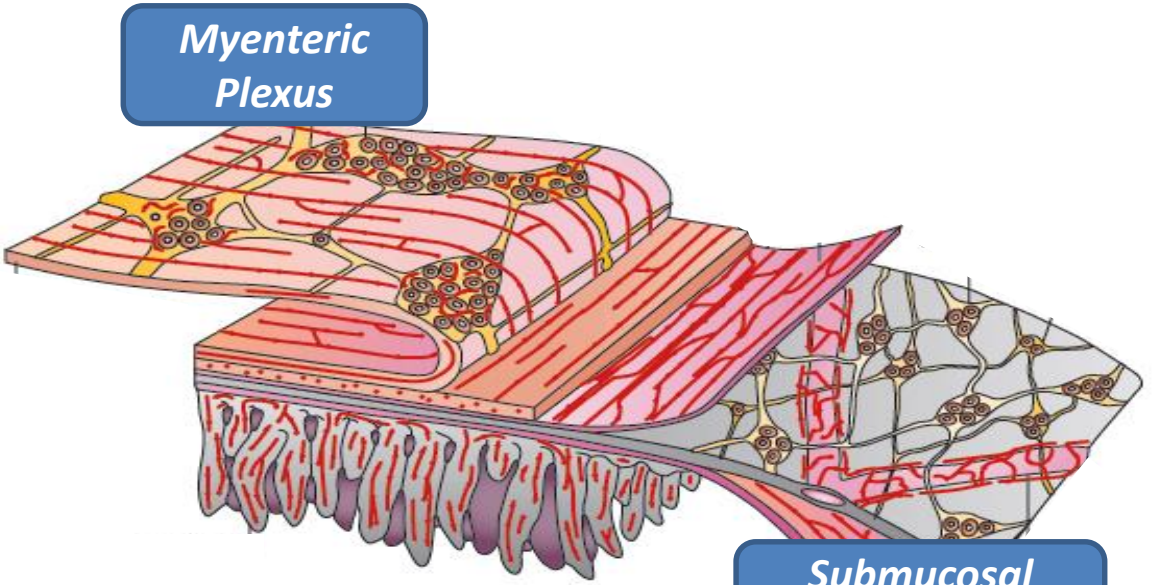
The gut-brain axis





from Pavlov's dog to the microbiota

Gut as « second brain »

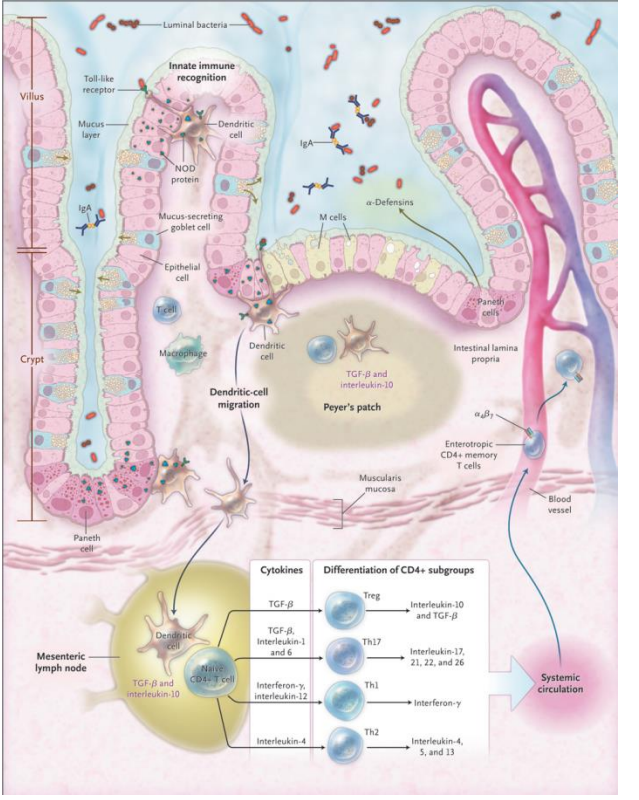


> 100 millions neurons

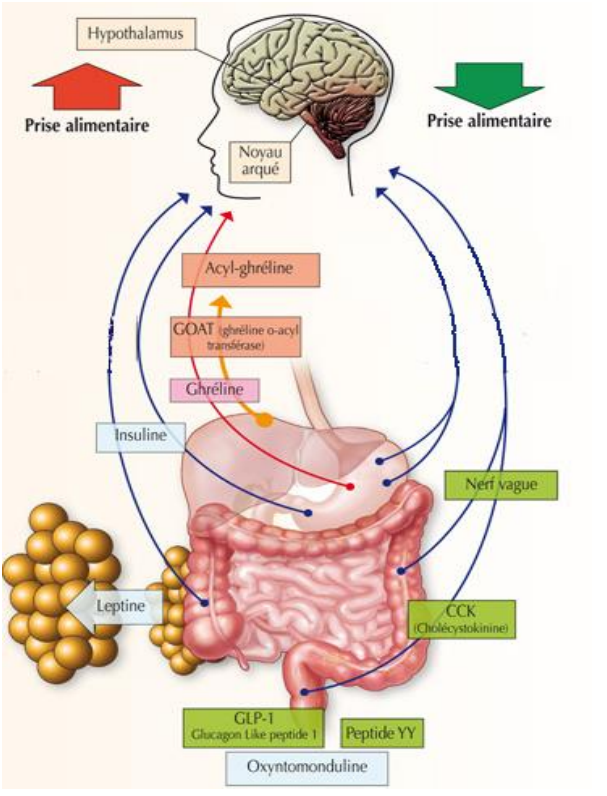
Schemann M et Neunlist M Neurogastroenterol Motil 2004,16 (suppl1) : 55-59

Intestinal immune system
Abraham et al

N Engl J Med 2009;361:2066-78.



Gut-Brain signals regulate food intake

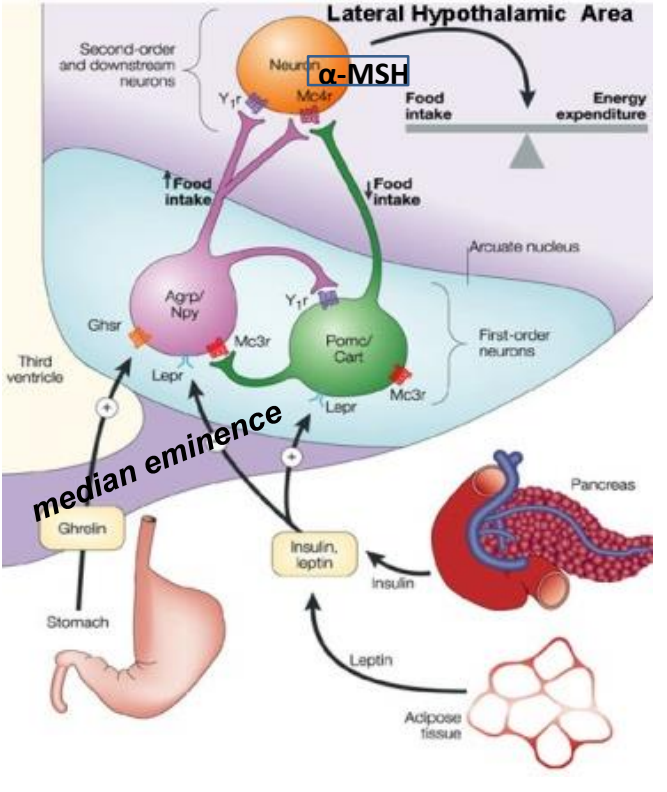


(Luquet, 2008)

Hypothalamic integration of peripheral and central signals

↓

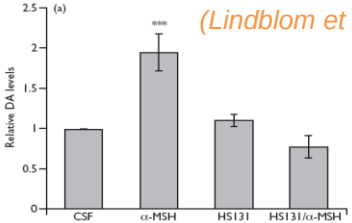
regulation of food intake



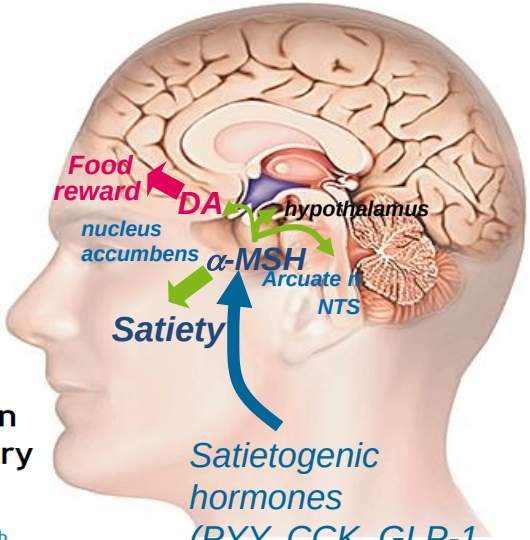
S. Barsh & M. Schwartz, Nature Rev., 2003

Central interactions between satiety and food-related pleasure

dopamine relase in n. accumbens



(Lindblom et al Neuroreport 2001)



Dopamine release in the lateral hypothalamus is stimulated by α-MSH in both the anticipatory and consummatory phases of feeding

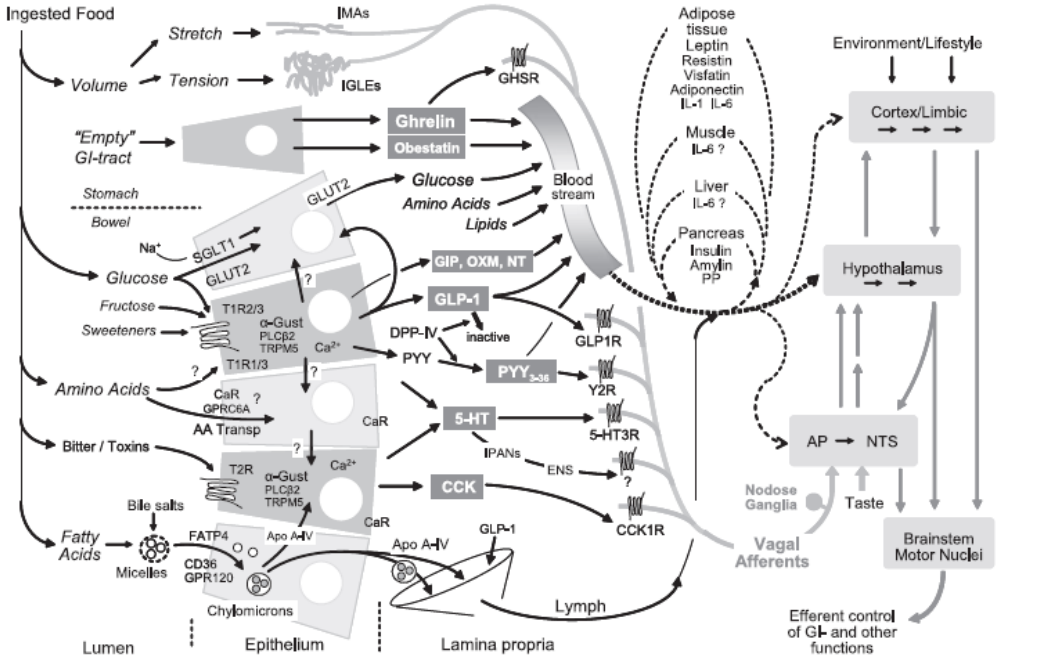
Romain Legrand[a,b], Nicolas Lucas[a,b], Jonathan Breton[a,b], Pierre Déchelotte[a,b,c], Sergueï O. Fetissov[a,b,*]

Psychoneuroendocrinology (2015) 56, 79—87

Vagal and hormonal gut–brain communication: from satiation to satisfaction

H.-R. BERTHOUD

Neurogastroenterol Motil (2008) **20** (Suppl. 1), 64–72



brain

↑

brain stem
spinal cord

↑

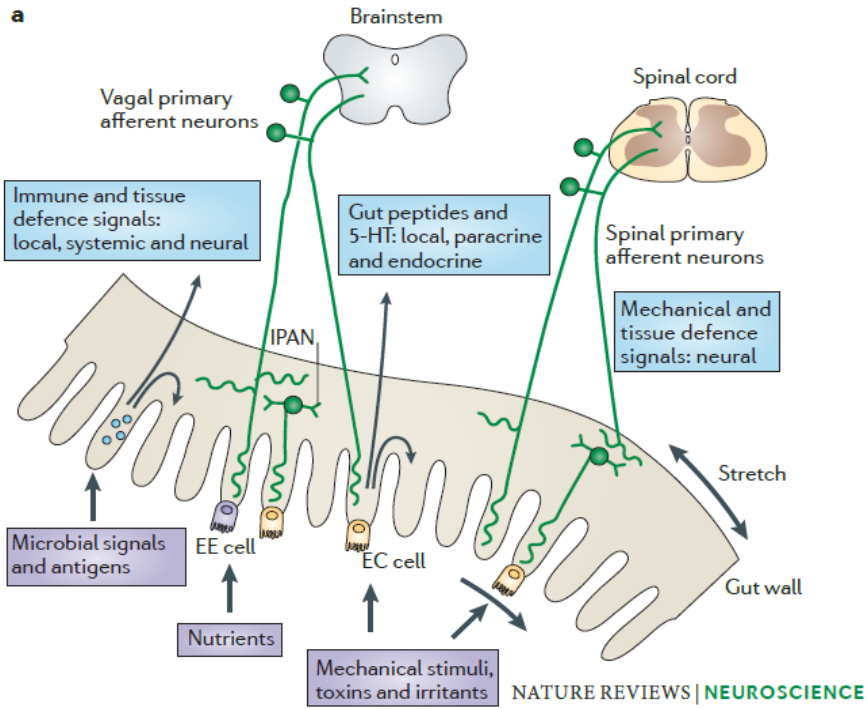
afferent nerves
peptides, amines
cytokines, LPS

↑

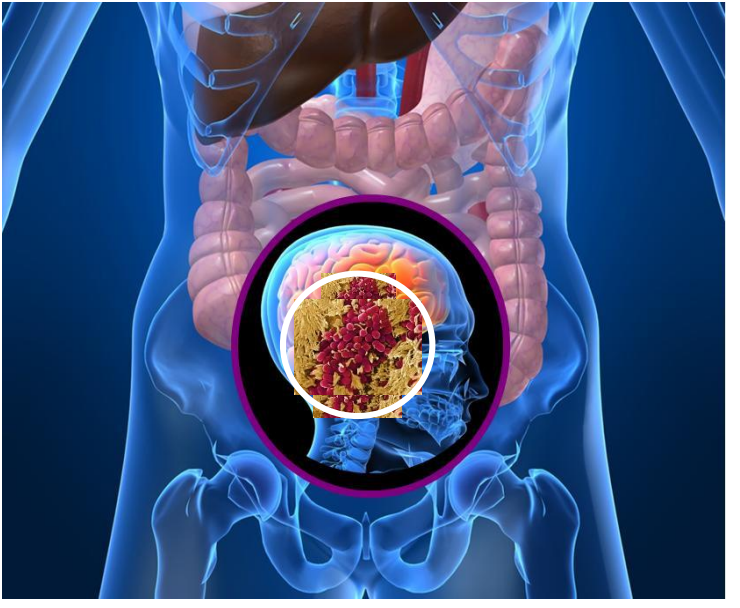
immune cells
epithelial layer
mucus

↑

nutrients,
metabolites,
microbiota ?

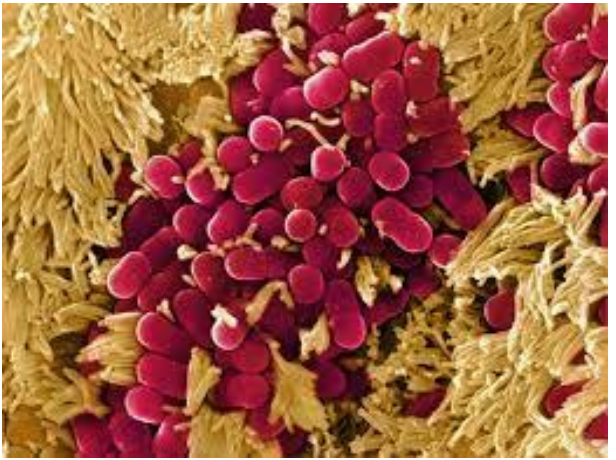


Microbiota as a « 3d brain »?



our « other genome» - « best friend » - « hidden driver »

2005 : the break-through of microbiota in nutrition



11070–11075 | PNAS | August 2, 2005 | vol. 102 | no. 31

Obesity alters gut microbial ecology

Ruth E. Ley[†], Fredrik Bäckhed[†], Peter Turnbaugh[†], Catherine A. Lozupone[‡], Robin D. Knight[§], and Jeffrey I. Gordon[†¶]

Human gut microbes associated with obesity

Ruth E. Ley, Peter J. Turnbaugh, Samuel Kleir
Jeffrey I. Gordon

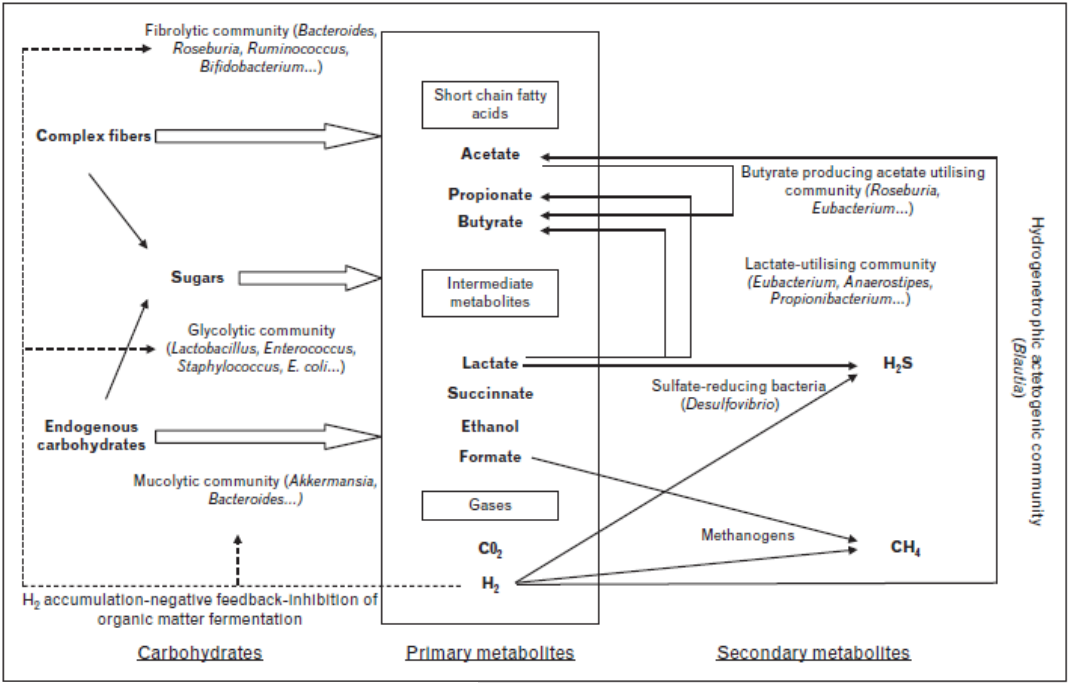
NATURE|Vol 444|21/28 December 2006

Vol 444|21/28 December 2006|doi:10.1038/nature05414

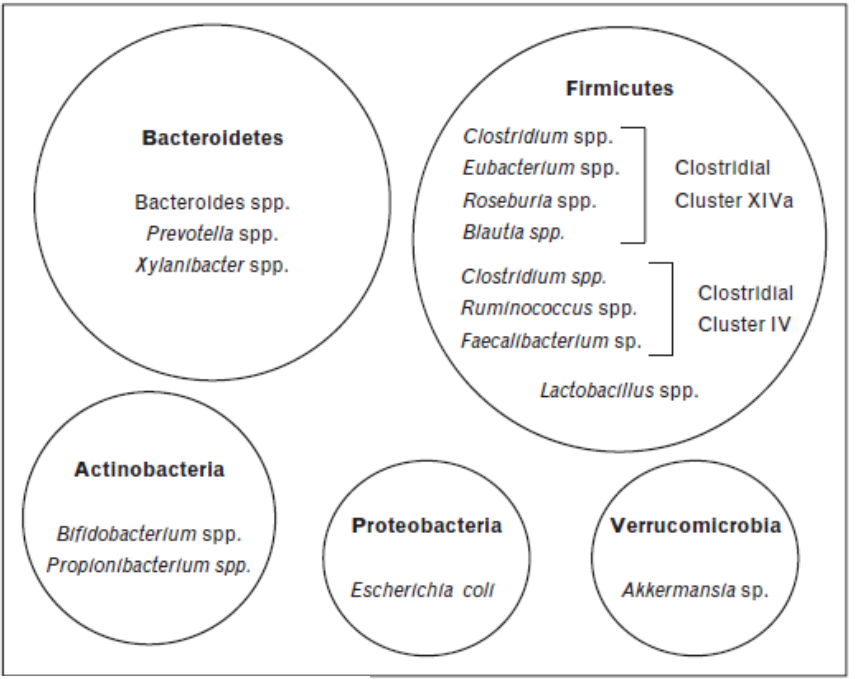
An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

Fermentation of carbohydrates by functional group of microbes of the human colonic microbiota.



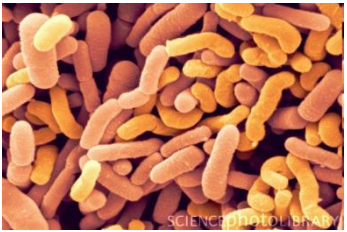
Predominant species of the human colonic microbiota.



Christophe Chassard and Christophe Lacroix **Curr Opin Clin Nutr Metab Care** 2013, 16:453–460

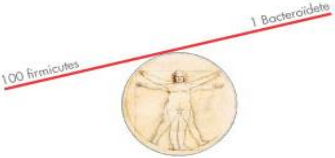
Microbiote intestinale et balance énergétique

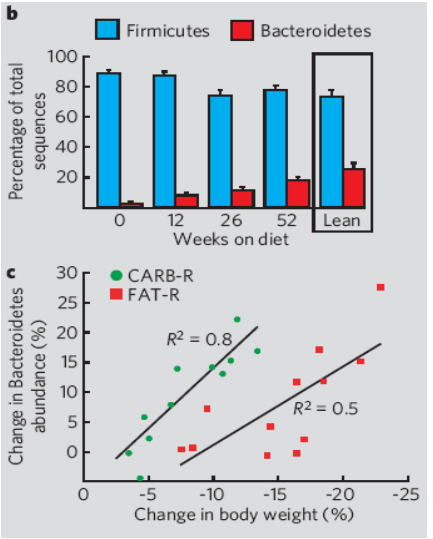
Les firmicutes : Gram-positives (lactobacilles)



Lactobacillus Acidophilus and L. Casei (yellow)

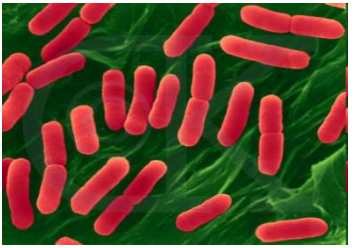
obese





Ley RE, Turnbaugh PJ, Klein S, Gordon JI. 2006. Microbial ecology: Human gut microbes associated with obesity. Nature 444(7122):1022-1023.

Les bacteroidetes: Gram-négatives (E.coli)

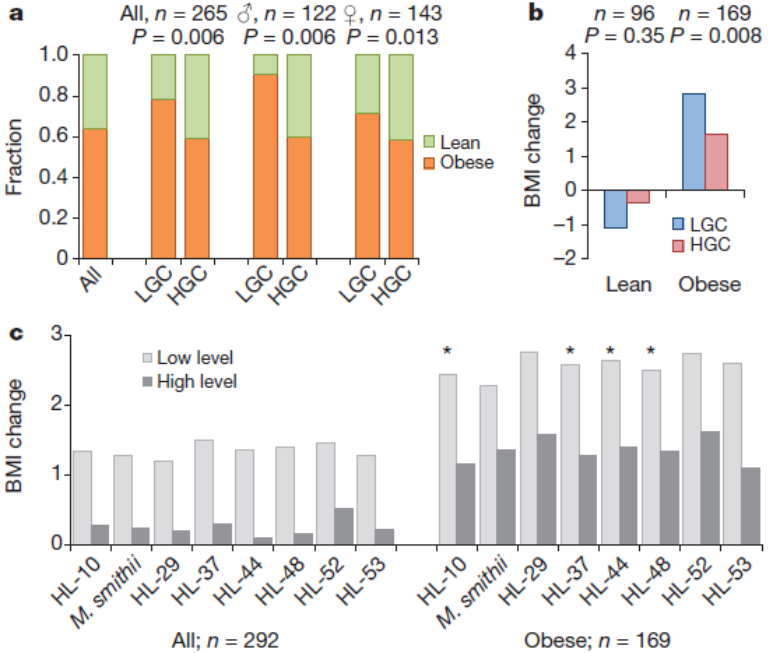


E.coli K12

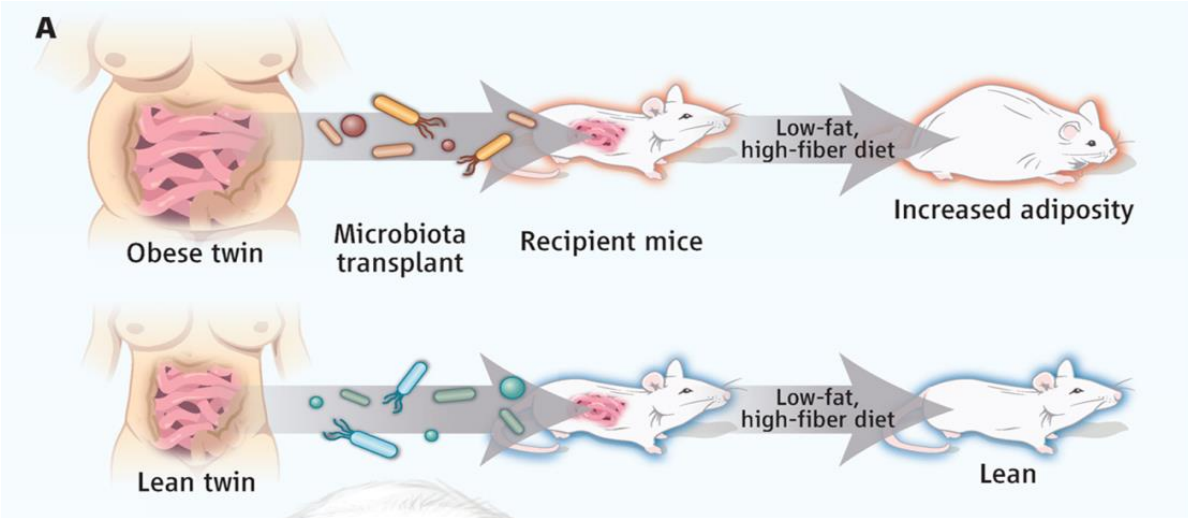
lean

Richness of human gut microbiome correlates with metabolic markers

Emmanuelle Le Chatelier[1]*, Trine Nielsen[2]*, 29 AUGUST 2013 | VOL 500 | NATURE | 541



Fecal microbiota transfer induces the phenotype…



Walker & Parkhill
Science 6 September 2013:
Vol. 341 no. 6150 pp. 1069-1070

Vagal and hormonal gut–brain communication: from satiation to satisfaction

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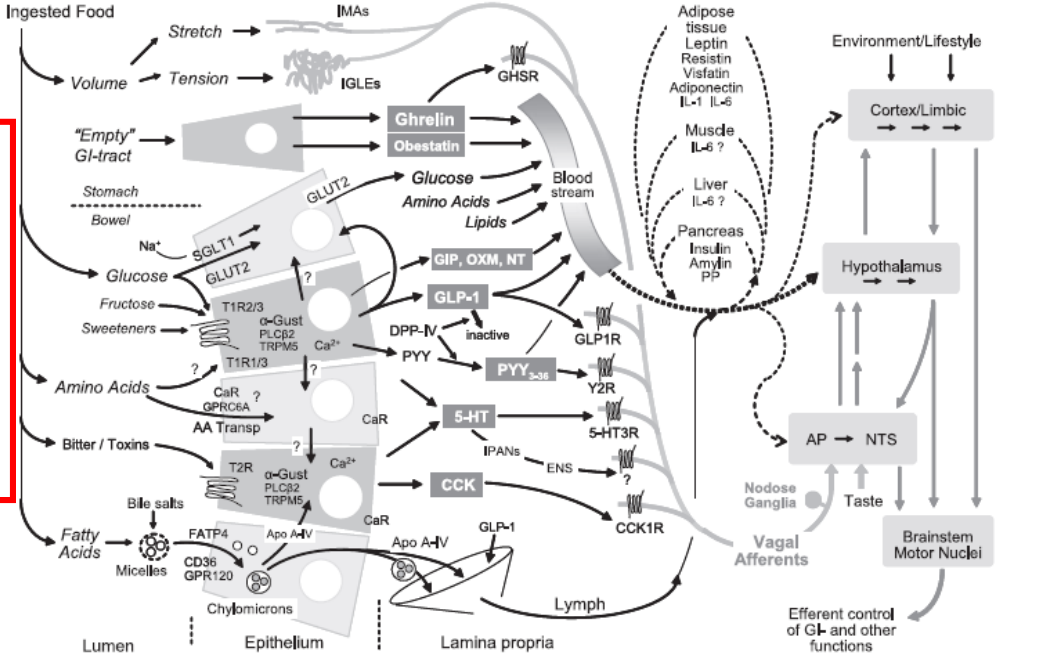
Neurogastroenterol Motil (2008) **20** (Suppl. 1), 64–72

Microbiota?



brain

↑

brain stem
spinal cord

↑

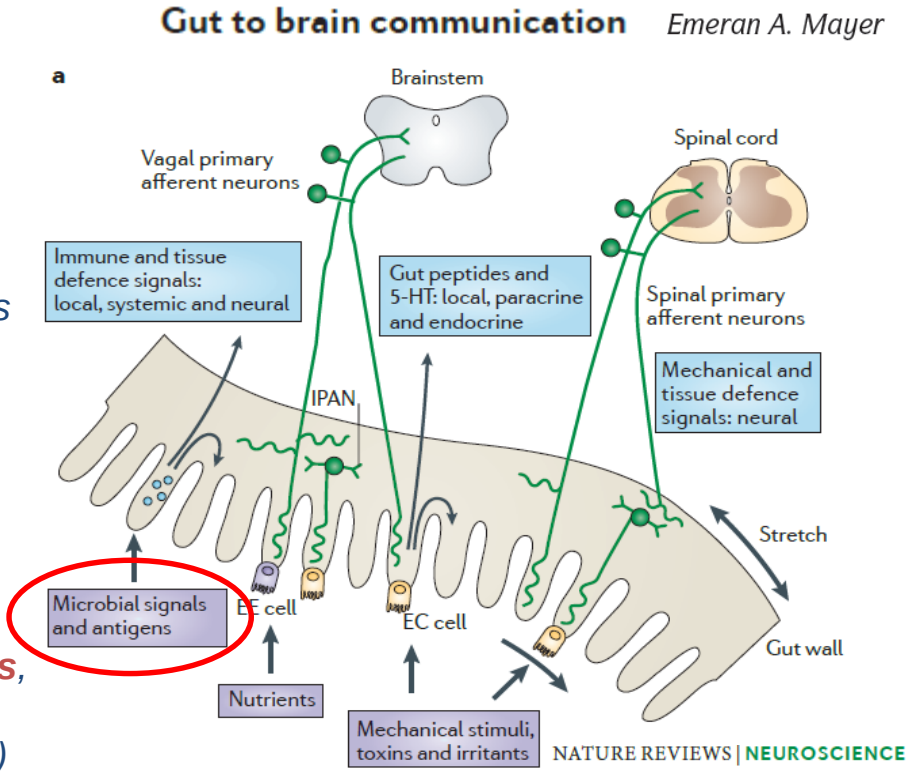
afferent nerves
peptides, amines
cytokines, LPS

↑

immune cells
epithelial layer
mucus

↑

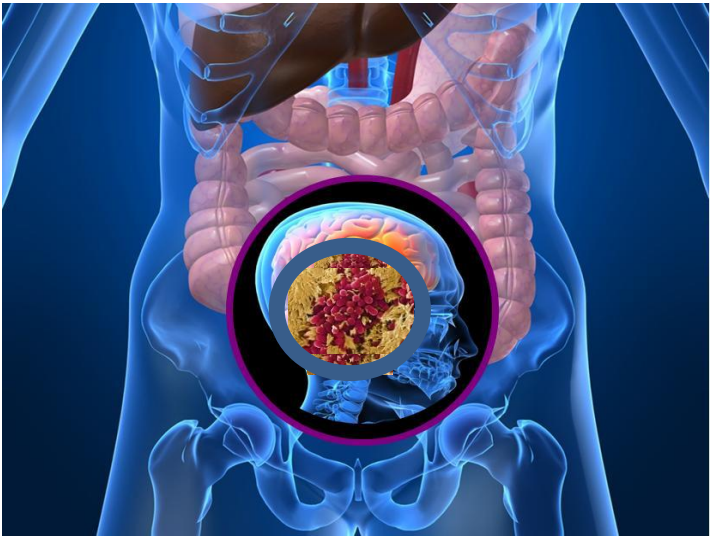
nutrients,
microbial signals,
(metabolites,
LPS, proteins…)



The microbiota: a major source of signals

- Toxins, endotoxins (LPS)
- quorum sensing molecules
- Short chain FA, branched SCFA
- proteins, peptides, glycoproteins
- Lipids (PG, LT) and derivatives
- Neurotransmitters (amines, glu, GABA)
- metabolites…

Disruption of MGBA: from harmony to disease



… which trigerring events ?

Stress as a Common Risk Factor for Obesity and Addiction

Rajita Sinha and Ania M. Jastreboff

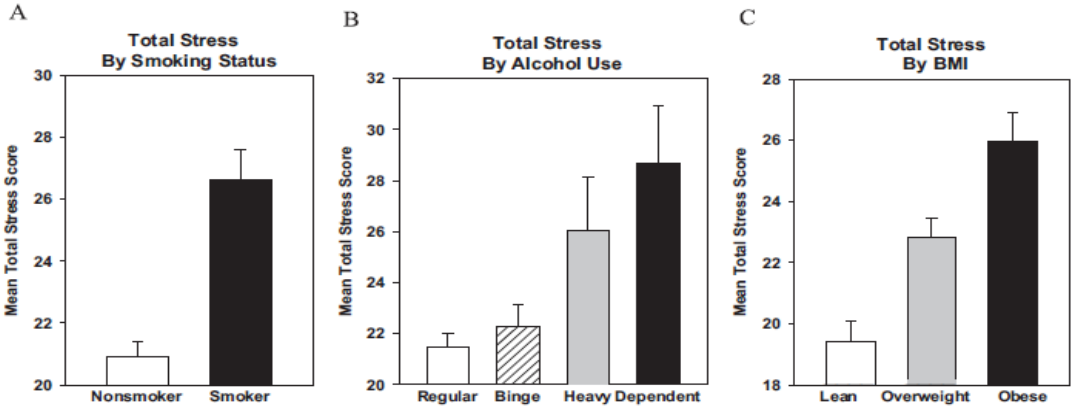


Figure 1. Total stress scores for cumulative adverse life events and chronic stress associated with **(A)** current smoking status [$\chi_1^2 = 31.66$, $p < .0001$; odds ratio (OR): 1.196 (95% confidence interval [CI]: 1.124–1.273)]; **(B)** current alcohol use as categorized by National Institute on Alcohol Abuse and Alcoholism criteria for regular, binge, and heavy levels of consumption and DSM-IV-R diagnosis for alcohol dependence [$\chi_1^2 = 15.37$, $p < .0001$; OR: 1.113 (95% CI: 1.055–1.173)]; and **(C)** current body mass index (BMI) groups for lean ($n = 206$), overweight ($n = 199$), and obese ($n = 183$) [$\chi_1^2 = 25.47$, $p < .0001$, OR: 1.146 (95% CI: 1.087–1.208)] assessed in a community sample of 588 participants.

Prevalence and association of perceived stress, substance use and behavioral addictions: a cross-sectional study among university students in France, 2009–2011

Marie Pierre Tavolacci[1,2*], Joel Ladner[2,3], Sebastien Grigioni[2,4], Laure Richard[4], Herve Villet[5] and Pierre Dechelotte[2,4]

→ High level of stress > Eating Disorders risk x 5 !

Table 4 Risk factors associated with perceived stress by quartile (logistic regression) (N = 1876)

	Q1 [0–09]	Q2 [10-15] AOR (95% CI)	p	Q3 [16-20] AOR (95% CI)	p	Q4 [>20] AOR (95% CI)	p
Male	1.00	0.58 [0.41-0.81]	0.0014	0.40 [0.28-0.57]	$<10^{-3}$	0.18 [0.11-0.26]	$<10^{-3}$
Curriculum							
Practice of sport	1.00	0.70 [0.51-0.97]	0.03	0.71 [0.51-1.00]	0.05	0.57 [0.39-0.80]	0.001
Regular smoker (≥1cigarette per day)	1.00	0.98 [0.67-1.43]	0.92	1.62 [1.11-2.36]	0.01	1.57 [1.04-2.37]	0.03
Regular alcohol user	1.00	0.87 [0.57-1.31]	0.49	0.64 [0.42-1.00]	0.05	0.63 [0.39-1.02]	0.06
Binge drinking	1.00	1.24 [0.76-2.05]	0.39	1.01 [0.60-1.71]	0.97	1.12 [0.62-2.03]	0.69
Alcohol abuse problems (Positive ADOSPA test)	1.00	1.32 [0.91-1.91]	0.14	1.65 [1.12-2.42]	0.01	2.22 [1.46-3.35]	0.0002
Drunkenness >10 per year	1.00	1.05 [0.65-1.68]	0.85	0.93 [0.57-1.54]	0.79	0.77 [0.43-1.36]	0.37
Eating disorders (positive Scoff)	1.00	1.61 [0.99-2.61]	0.05	2.72 [1.42-3.64]	0.0007	5.45 [3.42-8.69]	$<10^{-3}$
Risk of cyber addiction (Orman test)	1.00	1.58 [1.09-2.30]	0.01	2.02 [1.39-2.95]	0.0003	2.85 [1.90-4.28]	$<10^{-3}$

BMC Public Health 2013, **13**:724

Corticotropin-releasing hormone (CRH) regulates macromolecular permeability via mast cells in normal human colonic biopsies *in vitro*

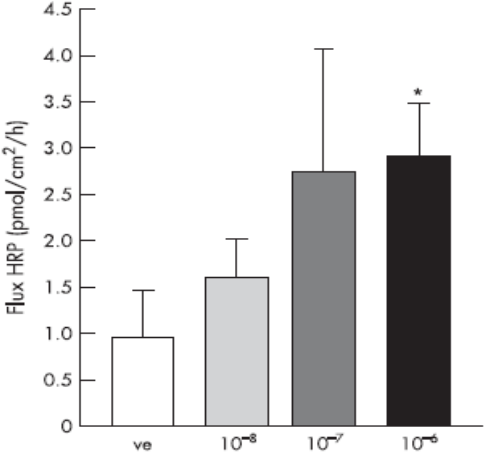


Figure 1 CRH exposure caused a dose-dependent increase in HRP permeation. There was a significant difference between CRH 10^{-6} mol/l (2.9 ± 0.5 pmol/cm²/h) compared to vehicle (ve) (1.0 ± 0.5); *ANOVA <0.05, $p = 0.0068$, Fischer PLSD. HRP uptake after exposure to CRH 10^{-8} mol/l (1.6 ± 0.4) or CRH 10^{-7} mol/l (2.7 ± 1.4) did not differ significantly from vehicle. Data are presented as mean $\pm$ SEM; $n = 6$ volunteers.

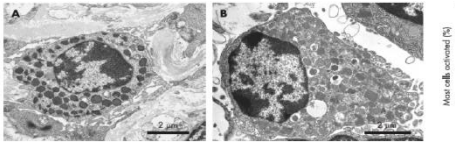


Figure 4 CRH exposure induced mast cell activation in human colon. Representative photomicrographs of sub-epithelial

Mast cells activated (%)

Wallon Gut 2008

The pathogenic potential of *Pseudomonas fluorescens* MFN1032 on enterocytes can be modulated by serotonin, substance P and epinephrine

Kelly Biaggini[1,2] · Corinne Barbey[1] · Valérie Borrel[1] · Marc Feuilloley[1] · Pierre Déchelotte[2] · Nathalie Connil[1]

Arch Microbiol (2015) 197:983–990

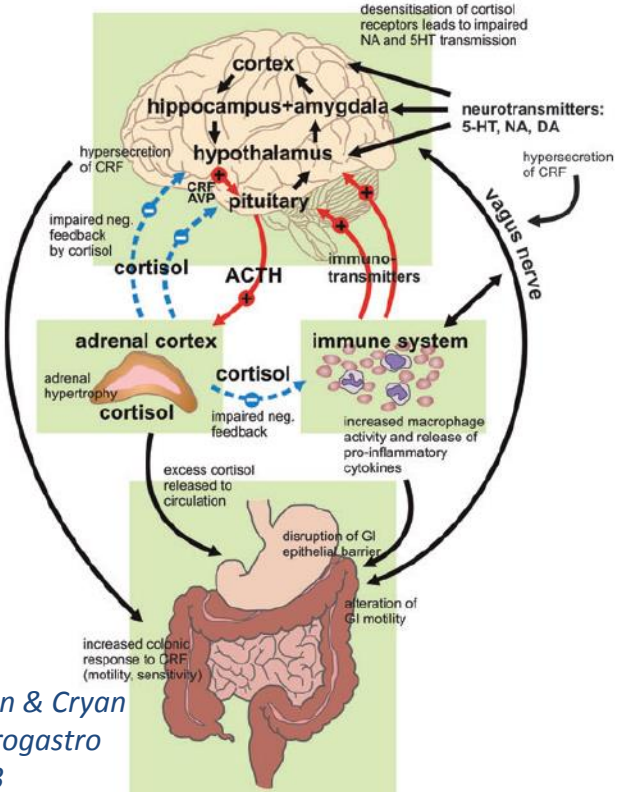
Biaggini *et al. Gut Pathog (2017) 9:20*
DOI 10.1186/s13099-017-0171-3

Gut Pathogens

Substance P enhances lactic acid and tyramine production in *Enterococcus faecalis* V583 and promotes its cytotoxic effect on intestinal Caco-2/TC7 cells

Kelly Biaggini[1†], Valérie Borrel[1†], Sabine Szunerits[2], Rabah Boukherroub[2], Awa N'Diaye[1], Arthur Zébré[1], Maryse Bonnin-Jusserand[3], Guillaume Duflos[4], Marc Feuilloley[1], Djamel Drider[5], Pierre Déchelotte[6] and Nathalie Connil[1*]

→ ***Neurotransmitters from the host impact microbiota behaviour***



Dinan & Cryan Neurogastro 2013

stress, microbiota, diet

↓

brain-gut axis dysfunction

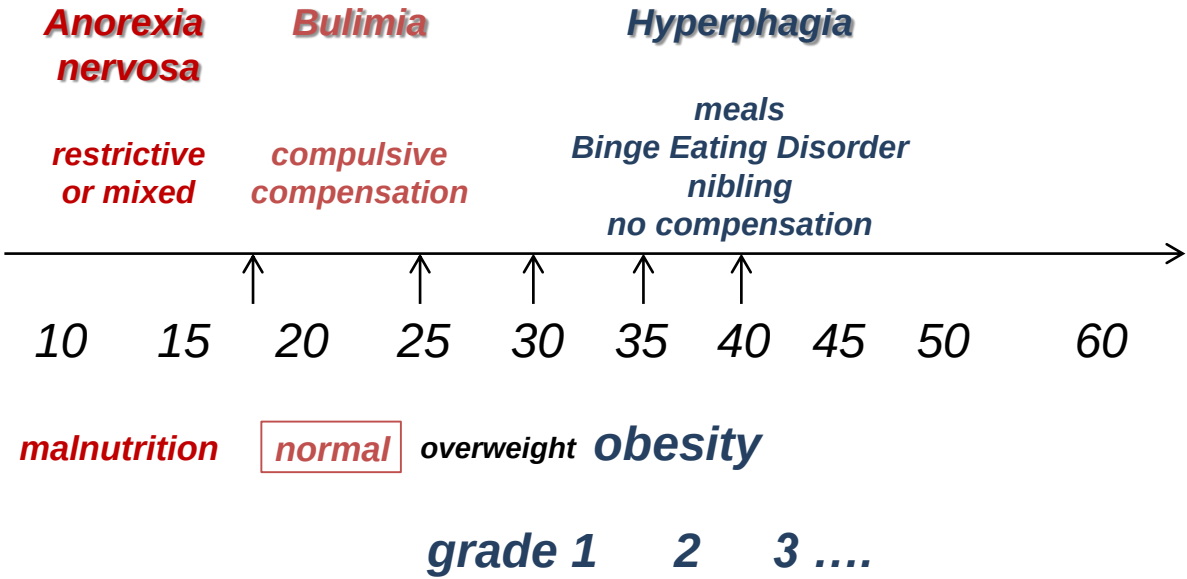
↓ ↑

weight control
appetite
inflammation
digestive functions
CNS : neuro-psy
peripheral organs

Relevance of the microbiota-gut-brain axis

- The microbiota-gut-brain axis
- **Weight and eating behaviour**
- Digestive diseases : IBD, IBS, Coeliac
- Neuropsychiatric disorders
- Perspectives and challenges

The spectrum of Eating Disorders



ED in the general population in Australia : x 2 1998-2008!

Table 2. Prevalence of eating disorder behaviors in 1998 and 2008.

	1998 survey (n = 3010)	2008 survey (n = 3034)			
	n (%)	n (%)	OR^{*} (95% CI)	χ^2	p
Any Behavior	130 (4.3%)	253 (8.4%)	2.3 (1.8–2.9)	41.4	0.00
Objective Binge Eating	80 (2.7%)	149 (4.9%)	2.2 (1.6–3.0)	21.0	0.00
Extreme Dieting	46 (1.5%)	101 (3.3%)	2.3 (1.6–3.4)	20.8	0.00
Purging	28 (0.9%)	29 (1.0%)	1.3 (0.7–2.5)	0.0	0.91

*OR = odds ratio; CI = confidence interval.

doi:10.1371/journal.pone.0048450.t002

D. Mitchison, PlosOne 2012

Prevalence of ED among french young adults (prevalence of obesity : 15%)

anorexia nervosa 1%

bulimia 4%

restrictive / mixed

RESTRICTIVE

COMPULSIVE

anorexia atypical 2%

hyperphagia 4%

BED

nibling 4%

MIXED

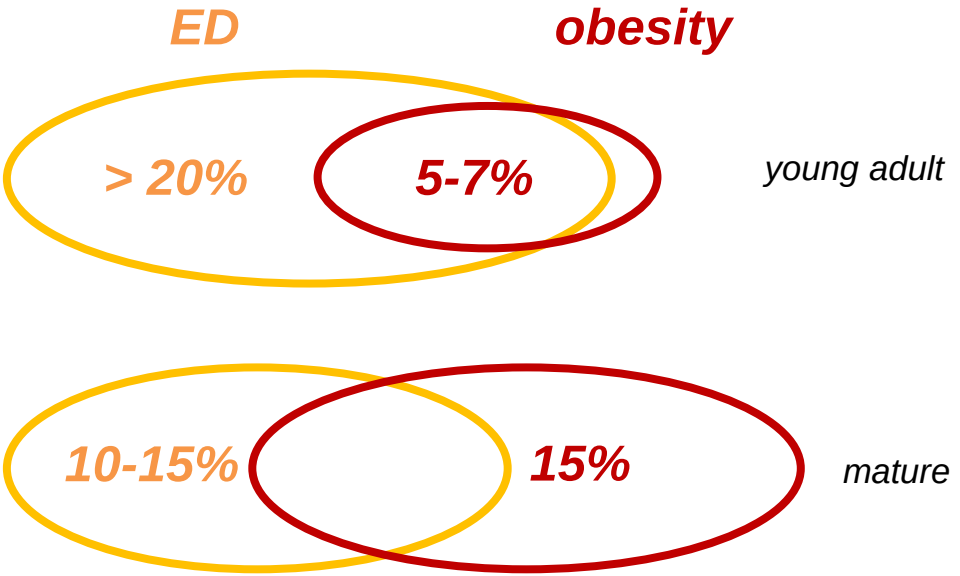
typical EDs

+

Atypical EDs

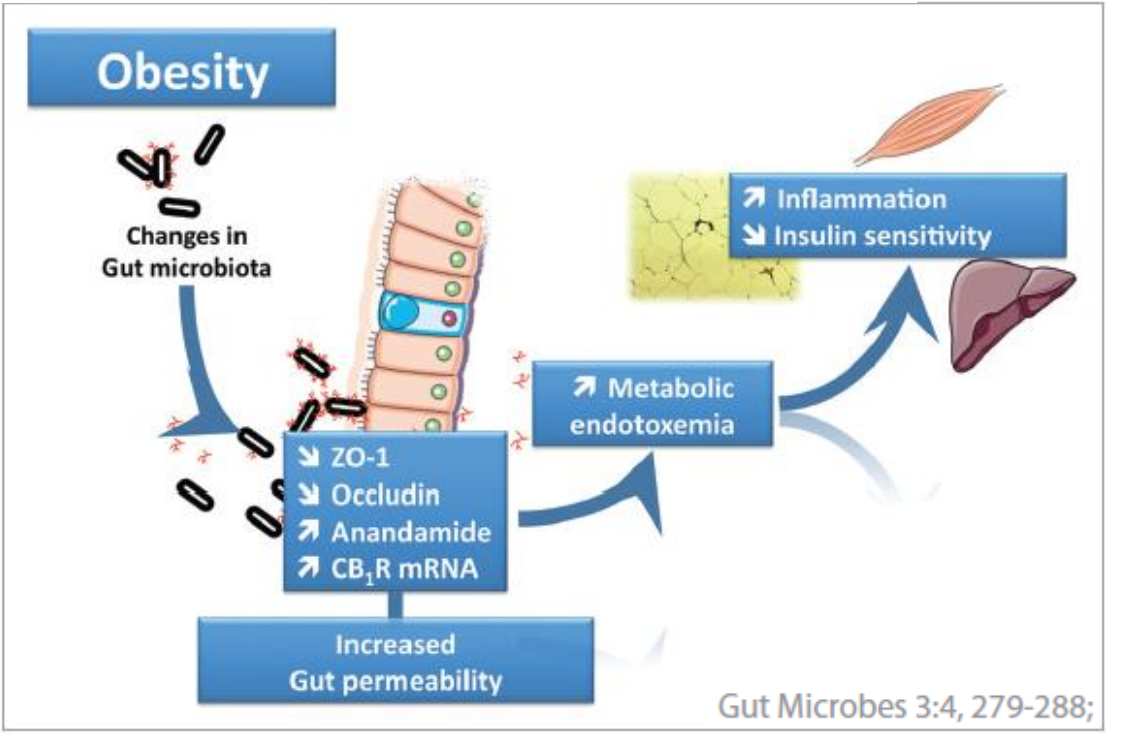
= total 15%

(P Déchelotte, unpublished)



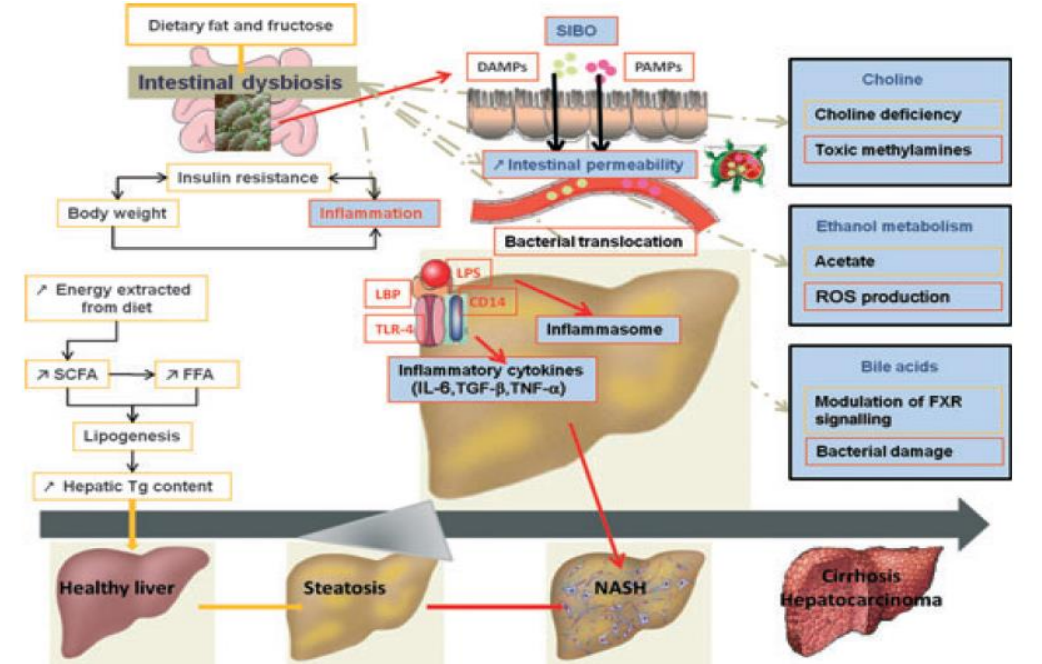
Total : 20-25% with either ED, obesity or both

Patrice D. Cani,* Melania Osto, Lucie Geurts and Amandine Everard



Gut Microbes 3:4, 279-288;

Gut microbiota and non-alcoholic fatty liver disease: new insights



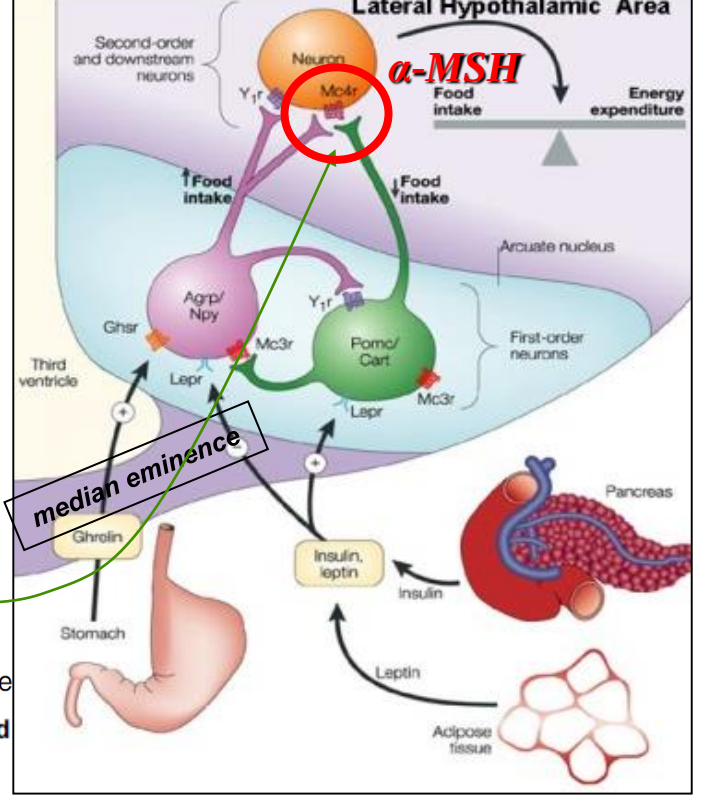
J. Aron-Wisnewsky[1,2], B. Gaborit[2,3,4,5,6], A. Dutour[3,4,5,6] and K. Clement[1,2] *Clin Microbiol Infect* 2013; **19**: 338–348

Immunoglobulins recognizing neuropeptides

↓

modulation of signaling

α-MSH Ig



Sergueï O. Fetissov and Pierre Déchelotte

Current Opinion in Clinical Nutrition and Metabolic Care 2008, 11:428–434

Autoantibodies against appetite-regulating peptide hormones and neuropeptides: Putative modulation by gut microflora

Sergueï O. Fetissov, M.D., Ph.D.[a,*], Maria Hamze Sinno, M.Sc.[a], Moïse Coëffier, Ph.D.[a,b], Christine Bole-Feysot, B.Sc.[a], Philippe Ducrotté, M.D., Ph.D.[a,c], Tomas Hökfelt, M.D.[d], and Pierre Déchelotte, M.D., Ph.D.[a,b]

Nutrition 24 (2008) 348–359

Igs against several appetite-regulating peptides are present in healthy women

- ***physiological regulatory function***
- ***intestinal origin***

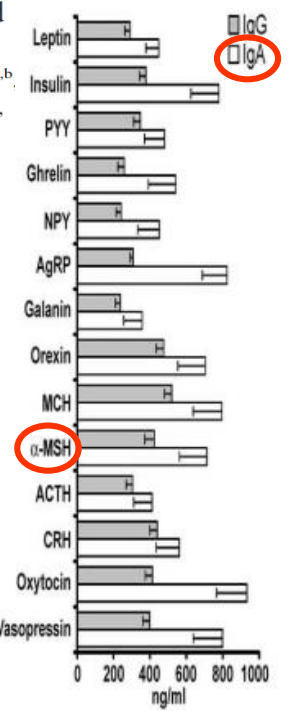


Table 1 Molecular mimicry of appetite-regulating peptide hormones and microbial proteins

α-MSH	*Bifidobacterium longum* (5 a. a.), *Bacteroides* (5 a. a.), *Bacillus cereus* (6 a. a.), *Escherichia coli* enteropathogenic and commensal strains (5 a. a.), Enterobacteria phage (5 a. a.), *Yarrowia lipolytica* (5 a. a.), *Candida albicans* (5 a. a.), *Cryptococcus neoformans* (5 a. a.). *Aspergillus fumigatus* (5 a. a.).
Ghrelin (24–51)	*Enterococcus faecalis* (7 a. a.), *Clostridium perfringens* (6 a. a.), *Lactobacillus casei* bacteriophage (5 a. a.), Mycobacteriophage (6 a. a.), *Saccharomyces cerevisiae* (5 a. a.), *Yarrowia lipolytica* (6 a. a.), *Candida albicans* (6 a. a.), *Cryptococcus neoformans* (7 a. a.).
Leptin (22–56)	*Lactococcus lactis* (7 a. a.), *Helicobacter pylori* (5 a. a.), *Campylobacter* (5 a. a.), *Lactobacillus* bacteriophage (5 a. a.), *Candida albicans* (7 a. a.), *Yarrowia lipolytica* (5 a. a.), *Aspergillus fumigatus* (6 a. a.).

nature COMMUNICATIONS

ARTICLE

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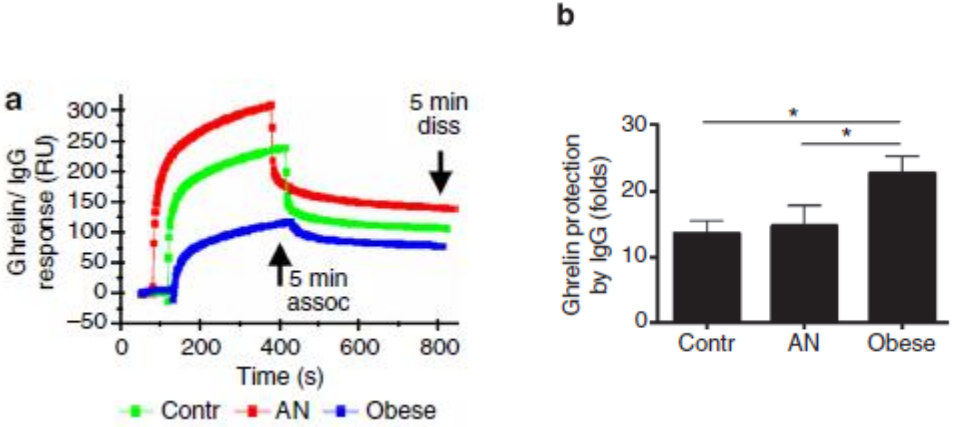
DOI: 10.1038/ncomms3685 OPEN

Anti-ghrelin immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans

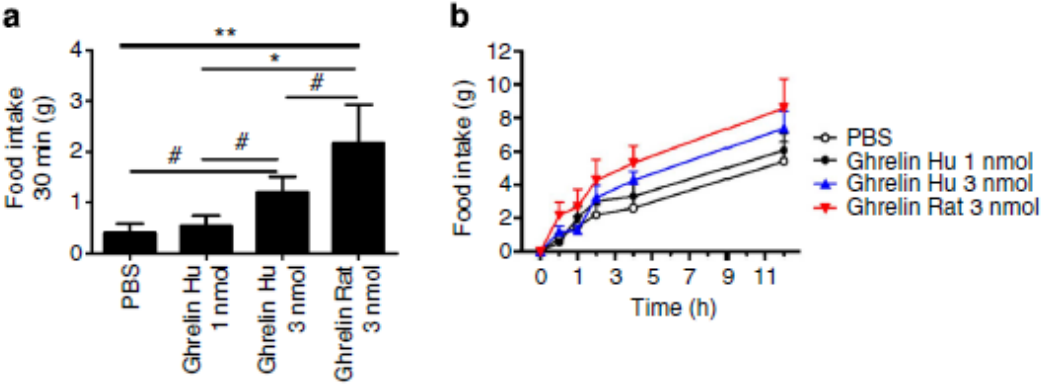
Kuniko Takagi[1,2,3,*], Romain Legrand[1,2,*], Akihiro Asakawa[3], Haruka Amitani[3], Marie François[1,2], Naouel Tennoune[1,2], Moïse Coëffier[1,2,4], Sophie Claeyssens[1,2,4], Jean-Claude do Rego[2,5], Pierre Déchelotte[1,2,4], Akio Inui[3] & Sergueï O. Fetissov[1,2]

Ghrelin antibodies from obese patients reduce ghrelin degradation



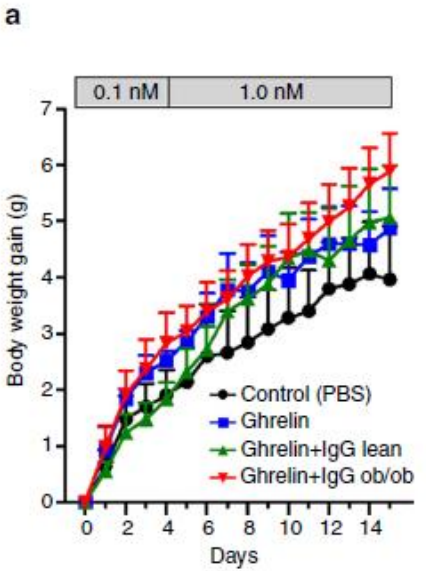
Takagi et al, Nat Comm 2013

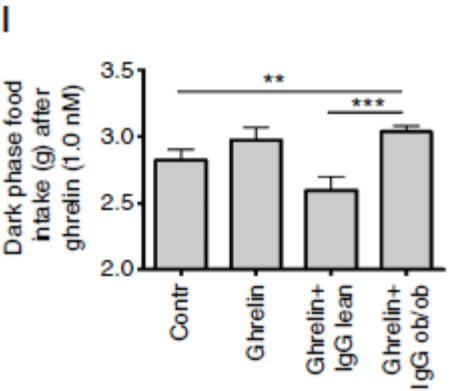
Transfer of Ghrelin antibodies from obese patients to mice increases food intake



Takagi et al, Nat Comm 2013

Transfer of ghrelin antibodies from ob/ob to naive mice increases food intake

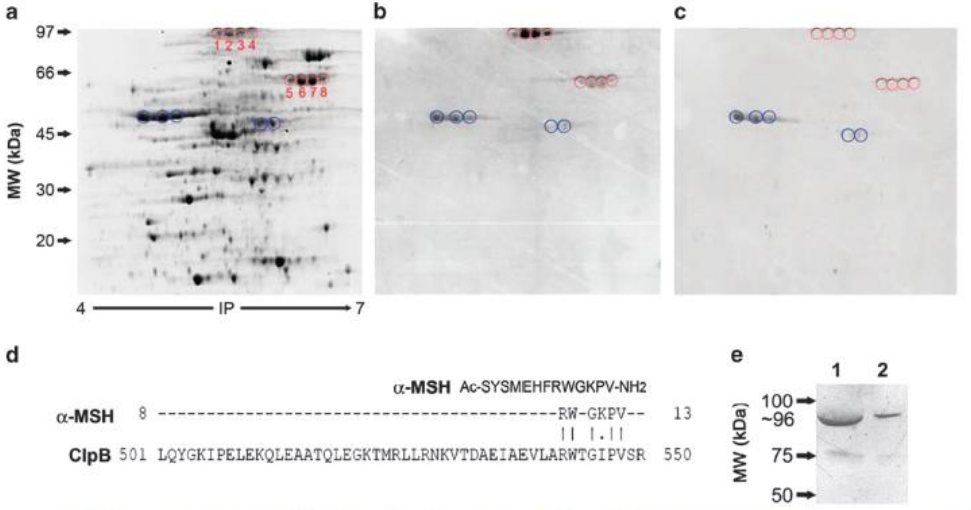




Takagi et al, Nat Comm 2013

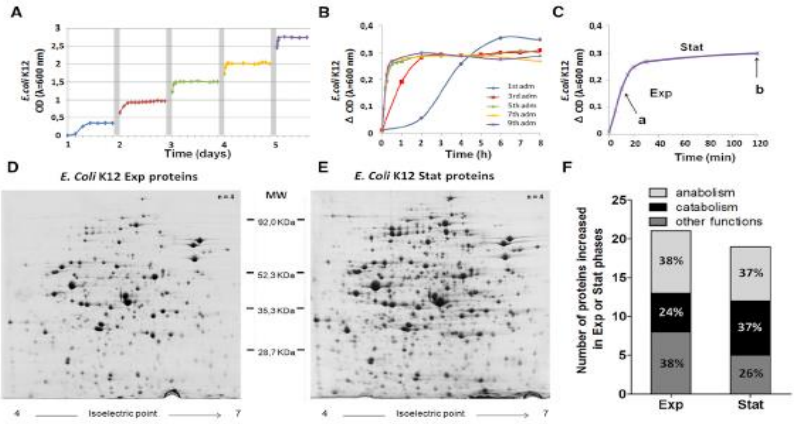
Bacterial ClpB heat-shock protein, an antigen-mimetic of the anorexigenic peptide α-MSH, at the origin of eating disorders

N Tennoune[1,2], P Chan[2,3], J Breton[1,2], R Legrand[1,2], YN Chabane[2,4], K Akkermann[5], A Järv[6], W Ouelaa[1,2], K Takagi[1,2], I Ghouzali[1,2], M Francois[1,2], N Lucas[1,2], C Bole-Feysot[1,2], M Pestel-Caron[2,7,8], J-C do Rego[2,9], D Vaudry[2,3], J Harro[5], E Dé[2,4], P Déchelotte[1,2,8] and SO Fetissov[1,2]



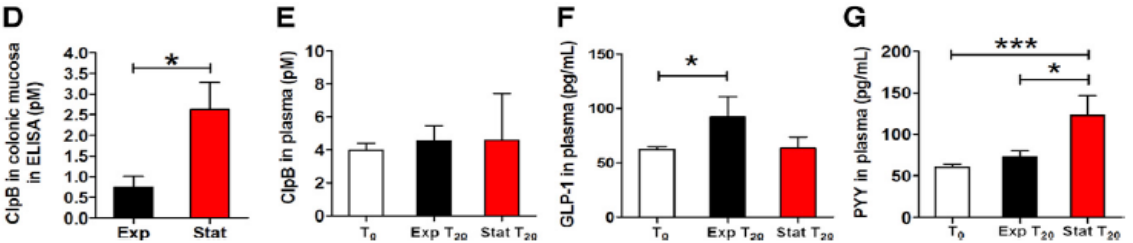
Gut Commensal *E. coli* Proteins Activate Host Satiety Pathways following Nutrient-Induced Bacterial Growth

Jonathan Breton,[1,5] Naouel Tennoune,[1,5] Nicolas Lucas,[1,5] Marie Francois,[1,5] Romain Legrand,[1,5] Justine Jacquemot,[1,5] Alexis Goichon,[1,5] Charlène Guérin,[1,5] Johann Peltier,[2,5] Martine Pestel-Caron,[2,5,6] Philippe Chan,[3,5] David Vaudry,[3,5] Jean-Claude do Rego,[4,5] Fabienne Liénard,[7] Luc Pénicaud,[7] Xavier Fioramonti,[7] Ivor S. Ebenezer,[8] Tomas Hökfelt,[9] Pierre Déchelotte,[1,5,6] and Sergueï O. Fetissov[1,5,*]



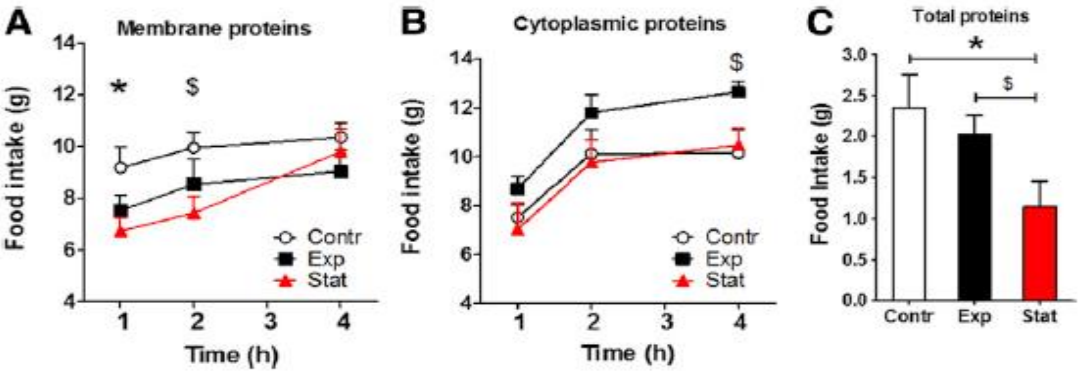
Breton et al, Cell Metabolism 2015

L'injection intracolique des protéines bactériennes stimule la libération d'hormones intestinales satiétogènes (GLP-1, PYY)



Breton et al, Cell Metabolism 2015

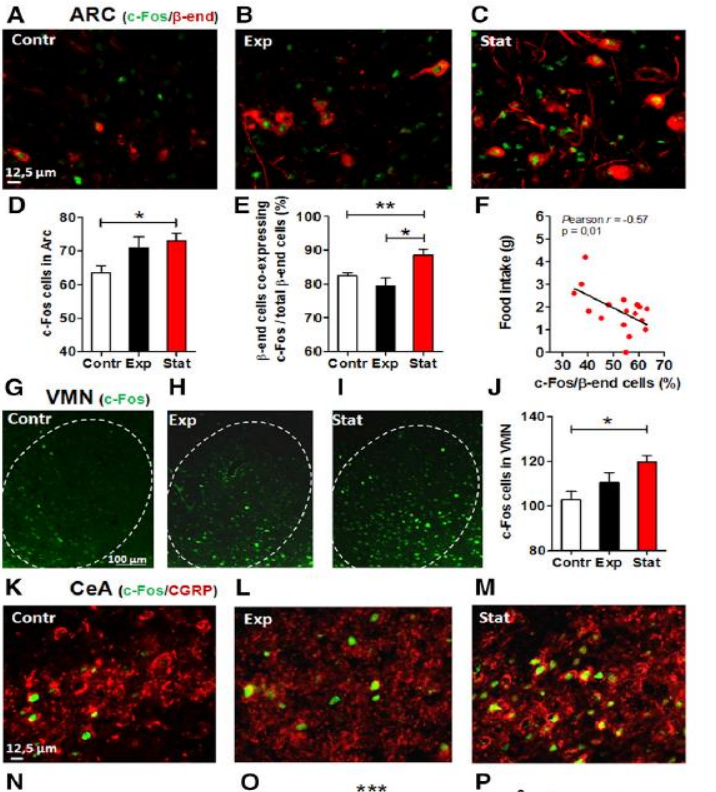
L'injection systémique (IP) des protéines bactériennes entraîne une réduction de la prise alimentaire…



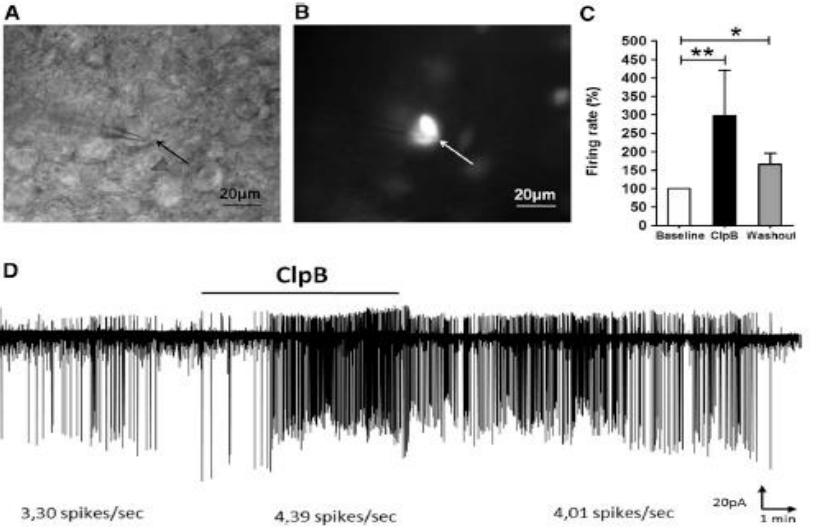
Breton et al, Cell Metabolism 2015

… et active les noyaux centraux impliqués dans la régulation de la prise alimentaire

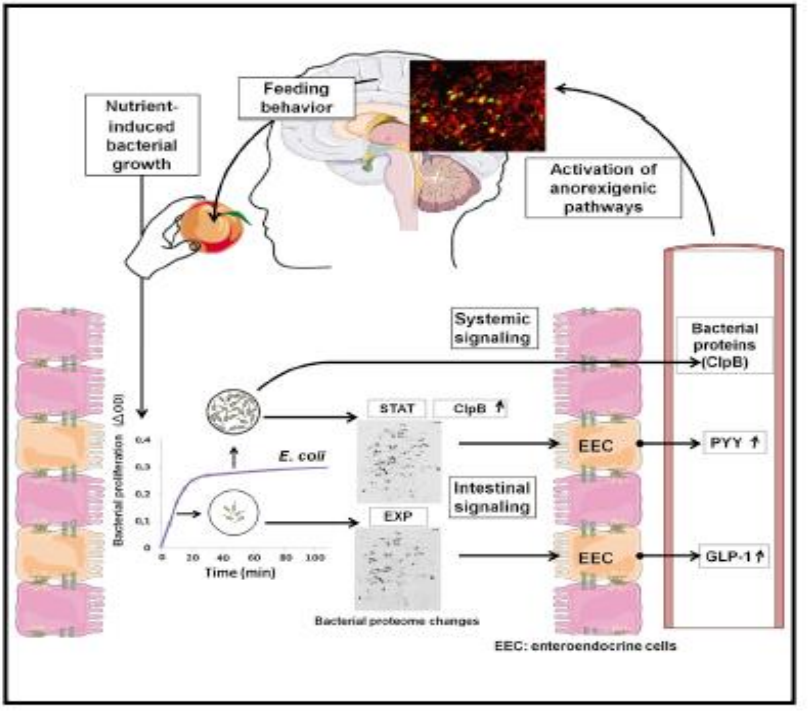
Breton et al,
Cell Metabolism 2015



ClpB, protéine bactérienne mimétique d'α-MSH, active les neurones à POMC du noyau arqué → effet satiétogène de type mélanocortine



Breton et al, Cell Metabolism 2015



Breton et al, Cell Metabolism 2015

The Melanocortin-4 Receptor Is Expressed in Enteroendocrine L Cells and Regulates the Release of Peptide YY and Glucagon-like Peptide 1 In Vivo

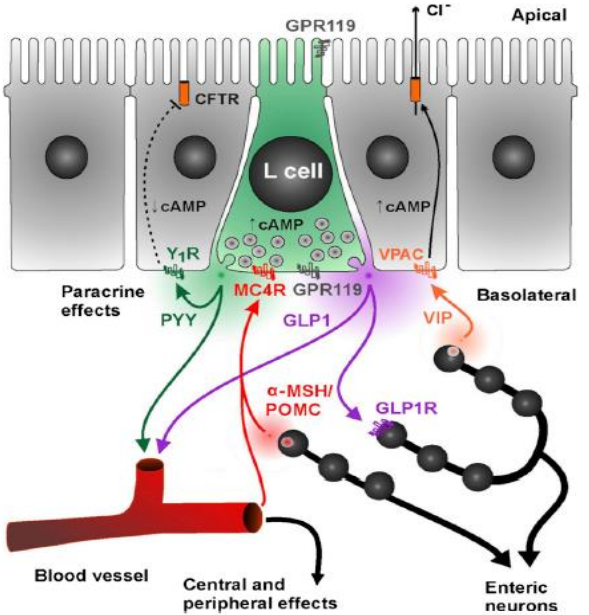


Figure 7. Regulation of GI Epithelial Function by MC4R Activation

Panaro et al
Cell Metabolism 2014

Monitoring Bacterial Community of Human Gut Microbiota Reveals an Increase in *Lactobacillus* in Obese Patients and *Methanogens* in Anorexic Patients

Fabrice Armougom[1], Mireille Henry[1], Bernard Vialettes[2], Denis Raccah[3], Didier Raoult[1]*

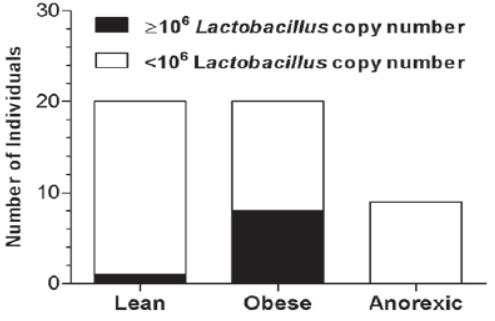


Figure 4. Distribution of high *Lactobacillus* concentrations. The number of individuals having a high *Lactobacillus* concentration was 1 out of 20, 8 out of 20, and 0 out of 9 for the lean, obese, and anorexic groups, respectively.

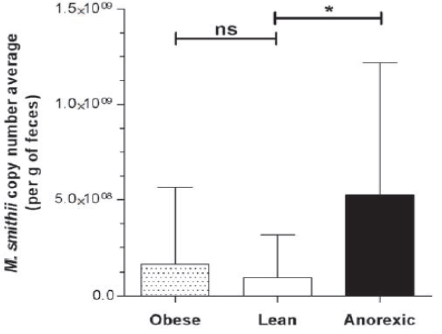


Figure 5. Quantification of the archaeon *M. smithii* species. Values are means±SD. P value <0.05 is represented as * and P value > 0.05 is indicated by "ns" for not significant.

Gut Dysbiosis in Patients with Anorexia Nervosa

Chihiro Morita[1], Hirokazu Tsuji[2], Tomokazu Hata[1], Motoharu Gondo[1], Shu Takakura[1], Keisuke Kawai[1], Kazufumi Yoshihara[1], Kiyohito Ogata[2], Koji Nomoto[2], Kouji Miyazaki[2], Nobuyuki Sudo[1]*

1 Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, **2** Yakult Central Institute, Tokyo, Japan

PLOS ONE | DOI:10.1371/journal.pone.0145274 December 18, 2015

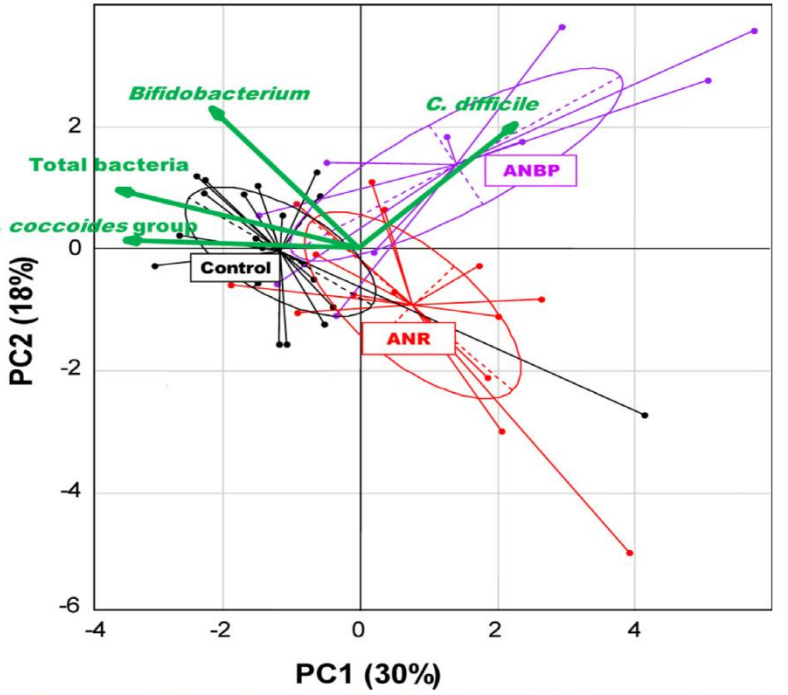


Fig 1. Principal component analysis (PCA) of bacterial counts in healthy female controls, 14 restrictive anorexia nervosa (ANR) patients, and 10 binge-eating anorexia nervosa (ANBP) patients. Black, red, and purple plots show data for the healthy female controls, ANR patients, and ANBP patients, respectively. The colored ellipse represents 50% of the samples. Arrows indicate the characteristic vectors of the upper 4 factor loadings. The numbers in parentheses represent the proportion of variance.

The Intestinal Microbiota in Acute Anorexia Nervosa and During Renourishment: Relationship to Depression, Anxiety, and Eating Disorder Psychopathology

Susan C. Kleiman, BSFS, Hunna J. Watson, PhD, Emily C. Bulik-Sullivan, Eun Young Huh, MS, Lisa M. Tarantino, PhD, Cynthia M. Bulik, PhD, and Ian M. Carroll, PhD

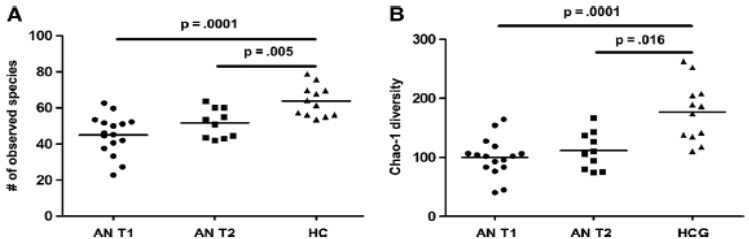
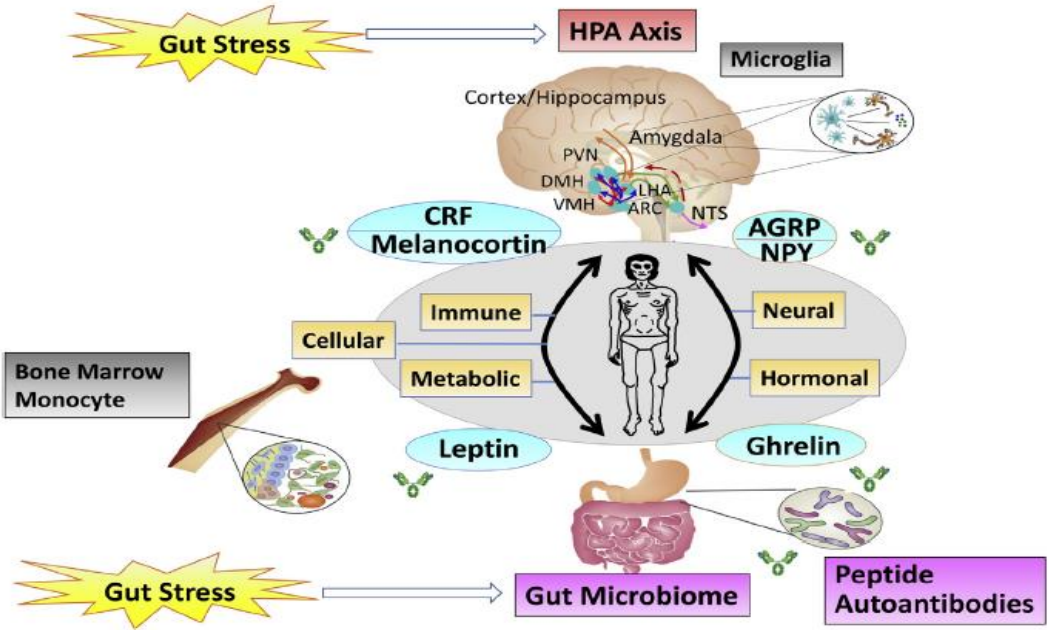


FIGURE 3. Alpha diversity in samples from patients with AN at hospital admission (T1; $n = 16$) and discharge (T2; $n = 10$) and an HCG ($n = 12$). Bacterial composition was characterized by 454 pyrosequencing of the 16S rRNA gene, and sequencing results were processed by the QIIME pipeline. Richness was characterized by the number of observed bacterial species in each sample (A) and Chao-1 estimator of diversity (B). Differences in alpha (within-sample) diversity were compared in AN T1 versus AN T2 versus HCG with two-tailed Wilcoxon-Mann-Whitney tests. At both time points (T1 and T2), the alpha diversity remained significantly lower in patients with AN versus HCG, measured as either the number of observed species or Chao-1 estimator. AN = anorexia nervosa; HCG = healthy comparison group; QIIME = Quantitative Insights Into Microbial Ecology; HC = healthy controls.

J Psychosom Medicine 2015

Microbiome, peptide autoantibodies, and eating disorders: A missing link between gut and brain

Inui et al, Nutrition 2015



Eating Disorders and microbiota: next steps?

- extend biological (neuropeptides, bacterial protein(s), immunoglobulins) and clinical profiling: large cohort study ongoing (Eating Disorders Inventory Longitudinal Survey

→ « theranostic » biomarkers (collaboration with TargEDys company)

- characterization of molecular peripheral / central mechanisms

- target modulation of gut barrier and microbiota to modulate behavior and prevent ED / restore homeostasis (dietary intervention + probiotics promoting satiety / appetite

Relevance of the microbiota-gut-brain axis

- The microbiota-gut-brain axis
- Weight and eating behaviour
- **Digestive diseases : IBD, IBS, Coeliac**
- Neuropsychiatric disorders
- Perspectives and challenges

Loss of diversity in microbiota is associated with increased risk of inflammatory bowel disease.

Manichanh, C. *et al.* Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* **55,** 205–211 (2006).
Lepage, P. *et al.* Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. *Gastroenterology* **141,** 227–236 (2011).

IBD: In Food We Trust

Journal of Crohn's and Colitis, 2016, 1351–1361

Rachel Marion-Letellier[a], Guillaume Savoye[a,b], Subrata Ghosh[c]

[a]INSERM Unit UMR1073, Rouen University and Rouen University Hospital, Rouen cedex, France [b]Department of Gastroenterology, Rouen University Hospital, Rouen cedex, France [c]Division of Gastroenterology, University of Calgary, Alberta, Canada

Brain-Gut Interactions in Inflammatory Bowel Disease

BRUNO L. BONAZ[1,2] and CHARLES N. BERNSTEIN[3]

GASTROENTEROLOGY 2013;144:36–49

environment + stress

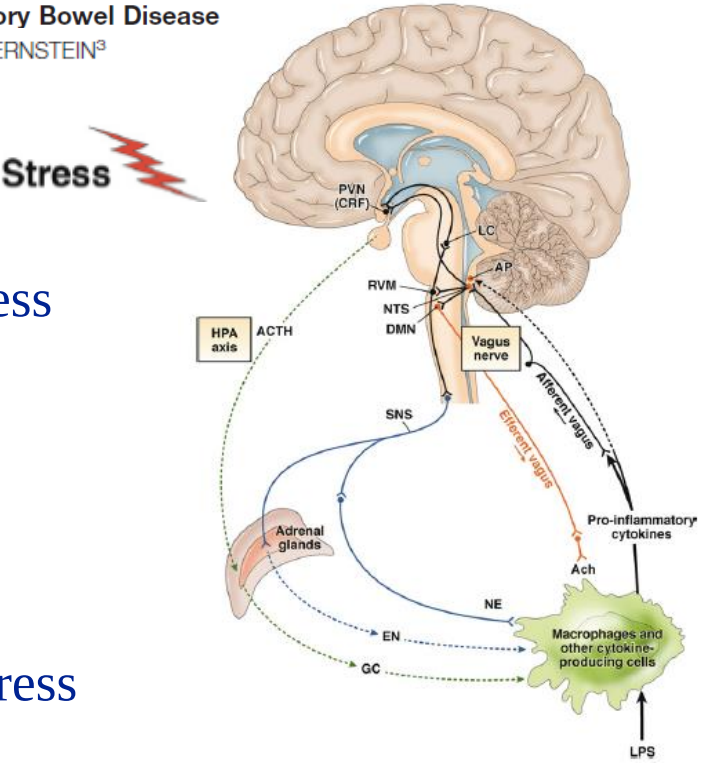
↓

IBD

↓

psychological distress

↑



Irritable Bowel Syndrome (IBS)

Recurrent abdominal pain

(or discomfort)

- ≥ 3 days per month during the last 3 months
- improved by defaecation

Alteration in bowel habits

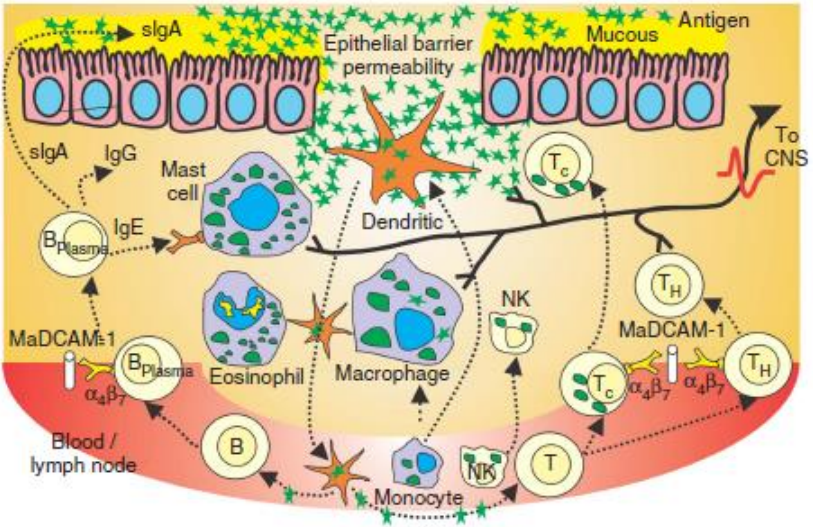
- Diarrhoea and/or constipation
- Change in stool frequency and/or stool form during pain exacerbation

Duration of symptoms > 6 months

Drossman DA et al Gastroenterology 2006;130:1377-90

Immune Activation in Irritable Bowel Syndrome: Can Neuroimmune Interactions Explain Symptoms?

Patrick A. Hughes, PhD[1–3], Heddy Zola[3,4], Irmeli A. Penttila, PhD[4–6], L. Ashley Blackshaw, PhD[1,7], Jane M. Andrews, MD, PhD[1,2] and Doreen Krumbiegel, PhD[3,4]



Am J Gastroenterol 2013; 108:1066–1074;

Increased Proteasome-Mediated Degradation of Occludin in Irritable Bowel Syndrome

Am J Gastroenterol 2010; 105:1181–1188

Moïse Coëffier, PhD[1,2], Romain Gloro, MD, PhD[3], Nabile Boukhettala, MSc[2], Moutaz Aziz, MD[4], Stéphane Lecleire, MD, PhD[2,5], Nathalie Vandaele, MD[5], Michel Antonietti, MD[5], Guillaume Savoye, MD, PhD[2,5], Christine Bôle-Feysot, BSc[2], Pierre Déchelotte, MD, PhD[1,2], Jean Marie Reimund, MD, PhD[3,6] and Philippe Ducrotté, MD, PhD[2,5]

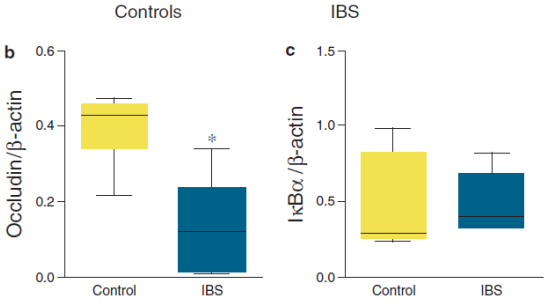


Figure 5. Expression of occludin (**a**, **b**) and IκBα (**a**, **c**) in colonic mucosa of control (n=8) and IBS (n=10) patients. Values are medians and interquartile ranges. *P<0.001 vs. controls. IBS, irritable bowel syndrome.

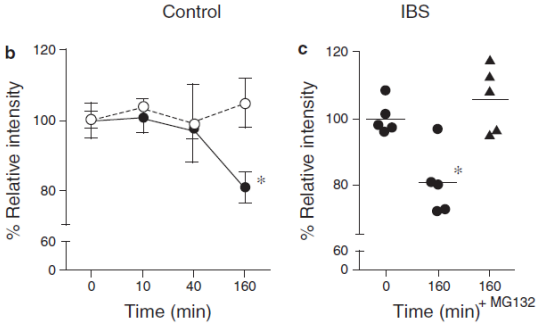
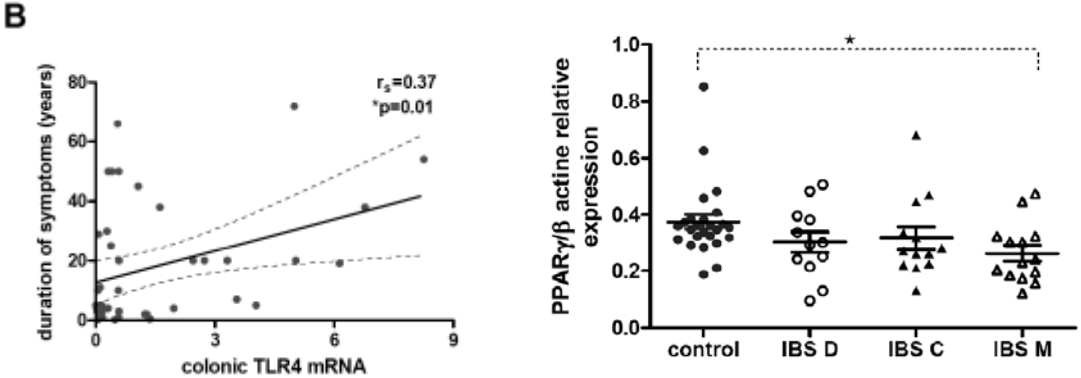


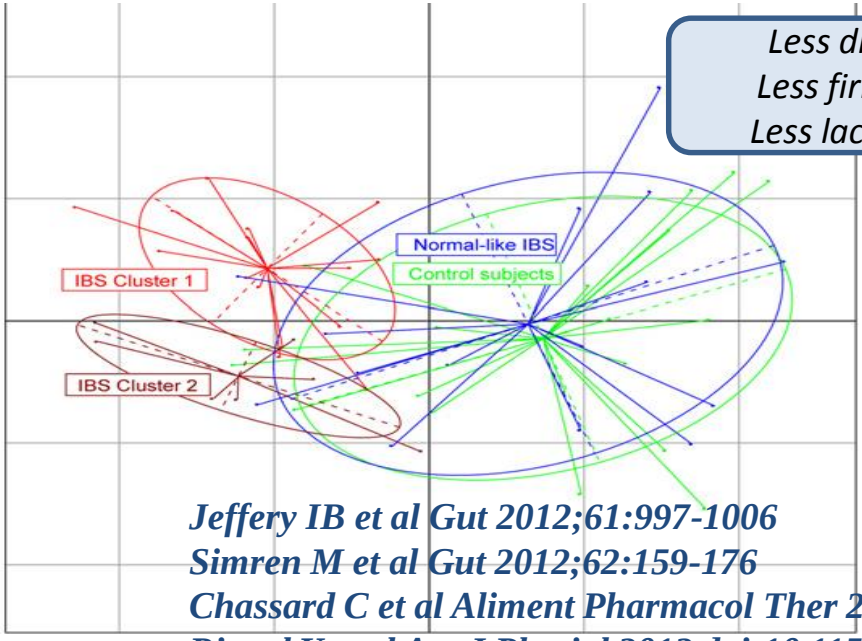
Figure 6. *In vitro* degradation assay for occludin. Recombinant human ^{35}S-occludin was incubated 0, 10, 40, or 160 min with colonic protein extracts from control (n=3) or IBS (n=5) patients. (**a**) Representative bands and (**b**) values (means±s.e.m.) for remaining ^{35}S-occludin. (**c**) Comparison of remaining ^{35}S-occludin incubated with colonic protein extracts from IBS patients for 0, 160 min and with colonic protein extracts from IBS patients plus proteasome inhibitor, MG132 at 10 μM for 160 min. *P<0.05 vs. others. IBS, irritable bowel syndrome.

Role of Toll Like Receptors in Irritable Bowel Syndrome: Differential Mucosal Immune Activation According to the Disease Subtype

Liliana Belmonte[1,2,3]*, Stéphanie Beutheu Youmba[1,2], Nathalie Bertiaux-Vandaële[4], Michel Antonietti[4], Stéphane Lecleire[1,2,4], Alberto Zalar[4], Guillaume Gourcerol[1,2,5], Anne-Marie Leroi[1,2,5], Pierre Déchelotte[1,2,6], Moïse Coëffier[1,2,6], Philippe Ducrotté[1,2,4]



Qualitative differences in faecal microbiota between IBS patients and controls



Less diversity
Less firmicutes
Less lactobacilli

Jeffery IB et al Gut 2012;61:997-1006
Simren M et al Gut 2012;62:159-176
Chassard C et al Aliment Pharmacol Ther 2012;1-11
Ringel Y et al Am J Physiol 2013 doi:10.1152

The Intestinal Microbiota and Immune Function in the Pathogenesis of Irritable Bowel Syndrome

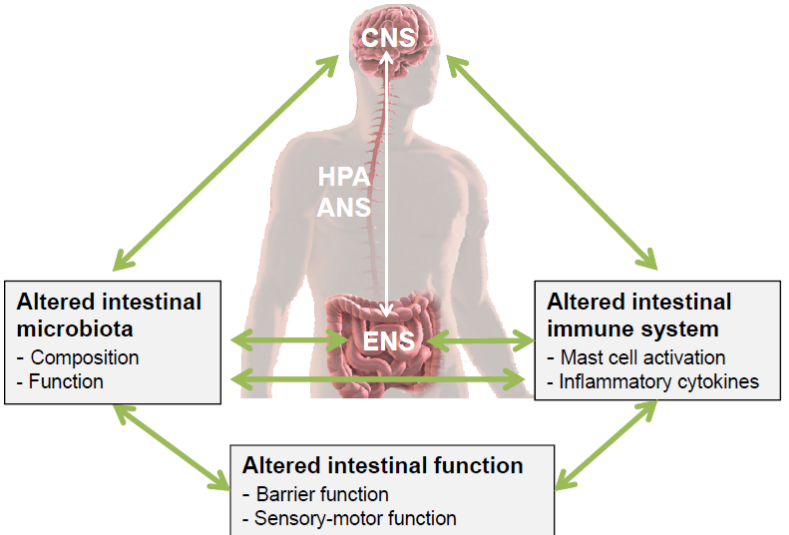
Triggers and predisposing factors

Environmental factors

Central:
- Psychological stress
- Anxiety/Depression

Peripheral
- Gastroenteritis
- Diet
- Medications
- Life habits

Host factors
- Genetics
- Disease conditions



Yehuda Ringel[1] and Nitsan Maharshak[1,2]

Am J Physiol Gastrointest Liver Physiol (July 25, 2013). doi:10.1152

Novel players in coeliac disease pathogenesis: role of the gut microbiota

Elena F. Verdu, Heather J. Galipeau and Bana Jabri

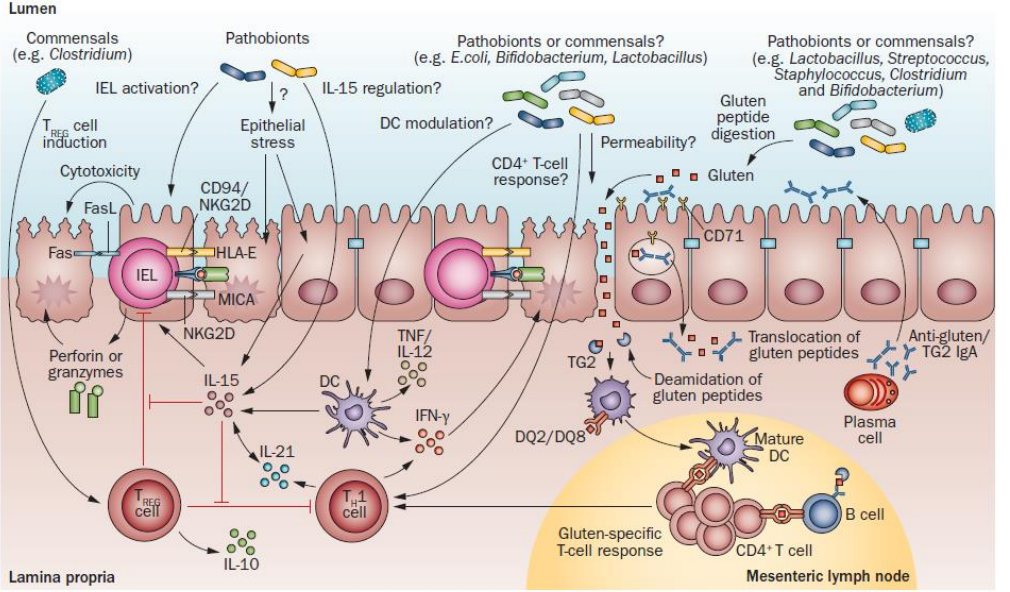


Figure 3 | Potential microbial modulation of coeliac disease pathogenesis. Gluten peptides in the small intestinal lumen

Humoral Immunity Links *Candida albicans* Infection and Celiac Disease

Corouge et al, Plos One 2015

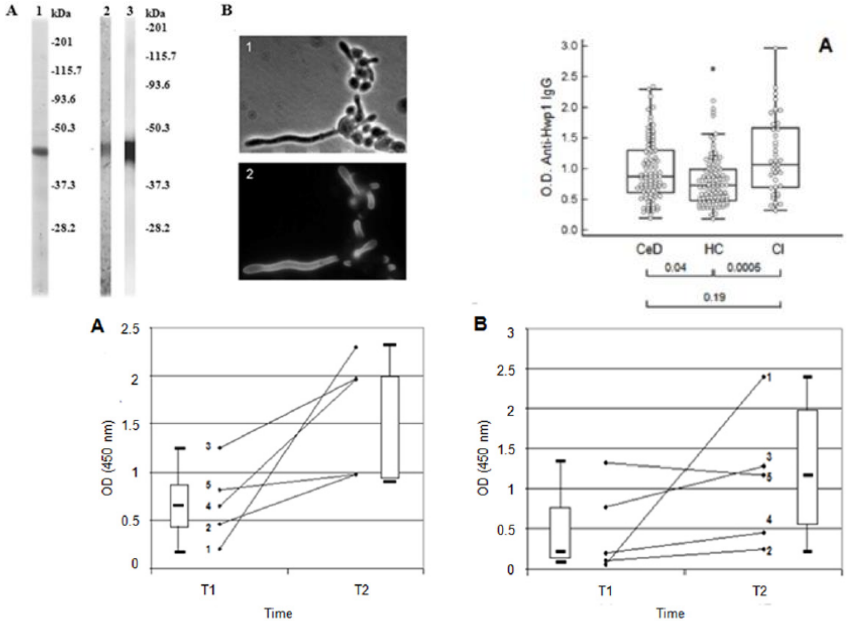


Fig 3. Kinetics of anti-Hwp1 and anti-gliadin antibody responses. (A) Anti-Hwp1 and **(B)** anti-gliadin antibodies in five patients with invasive *C. albicans* infection (CI) selected for having an increase in anti-Hwp1 IgG during infection. Each number represents a patient and the results are expressed as optical density. The anti-Hwp1 response parallels the anti-gliadin response (Box Plots) except in one patient (no. 5).

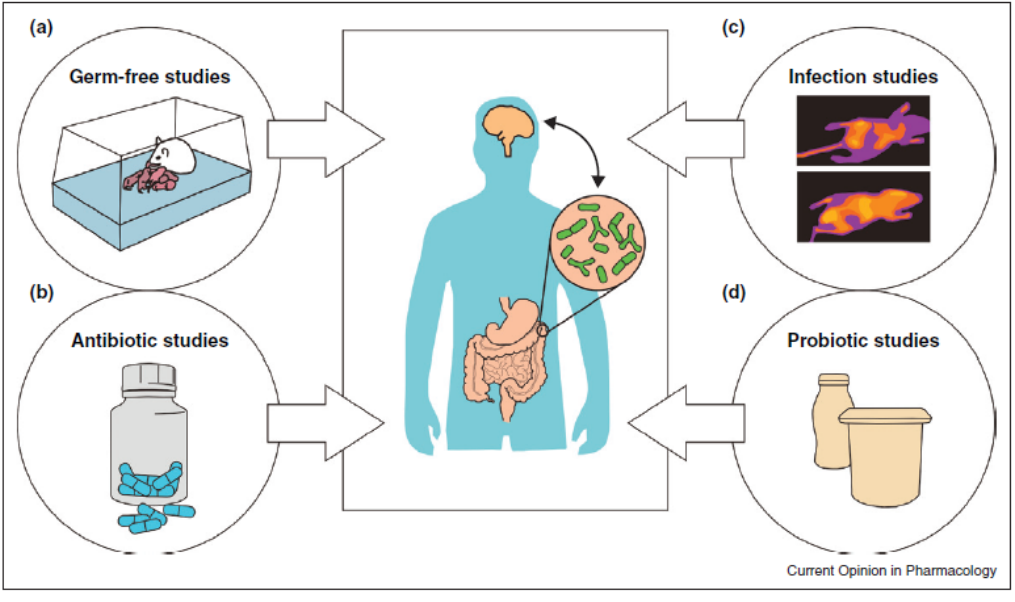
Relevance of the microbiota-gut-brain axis

- The microbiota-gut-brain axis
- Weight and eating behaviour
- Digestive diseases : IBD, IBS, Coeliac
- **Neuropsychiatric disorders**
- Perspectives and challenges

Communication between gastrointestinal bacteria and the nervous system

Current Opinion in Pharmacology 2012, 12:667–672

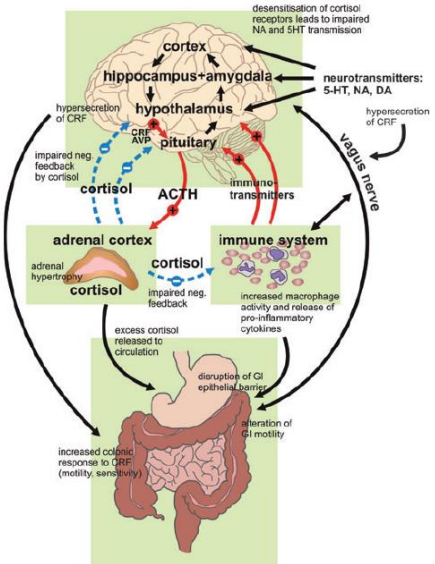
Javier A Bravo[1], Marcela Julio-Pieper[1], Paul Forsythe[2,3], Wolfgang Kunze[4], Timothy G Dinan[6,8], John Bienenstock[2,5] and John F Cryan[7,8]



Melancholic microbes: a link between gut microbiota and depression?

T. G. DINAN & J. F. CRYAN

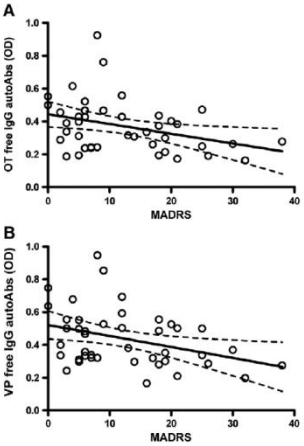
Neurogastroenterol Motil (2013) **25**, 713–719



- Overlap IBS / ADD / OCD
- L. rhamnosus reduces anxiety in mice (GABA, vagal pathway)
- B. infantis, L. helveticus, B. Longum NCC3001: beneficial effects on anxiety and depression in models
- other microorganisms (funghi) implicated
- limited data in humans

Autoantibodies reacting with vasopressin and oxytocin in relation to cortisol secretion in mild and moderate depression

Frederico Duarte Garcia [a], Quentin Coquerel [a], Evelyn Kiive [b], Pierre Déchelotte [a], Jaanus Harro [b], Sergueï O. Fetissov [a,*]



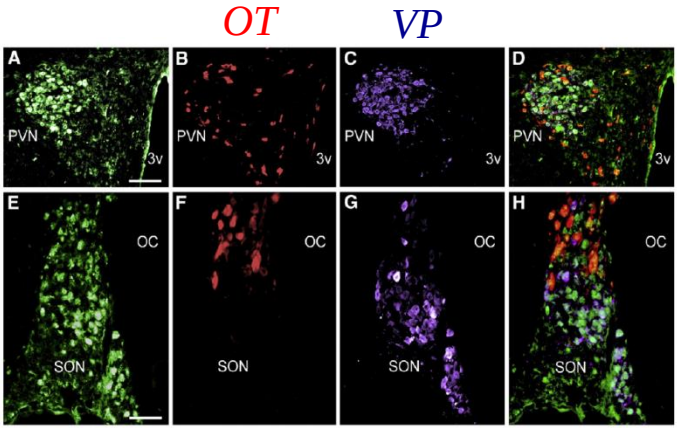


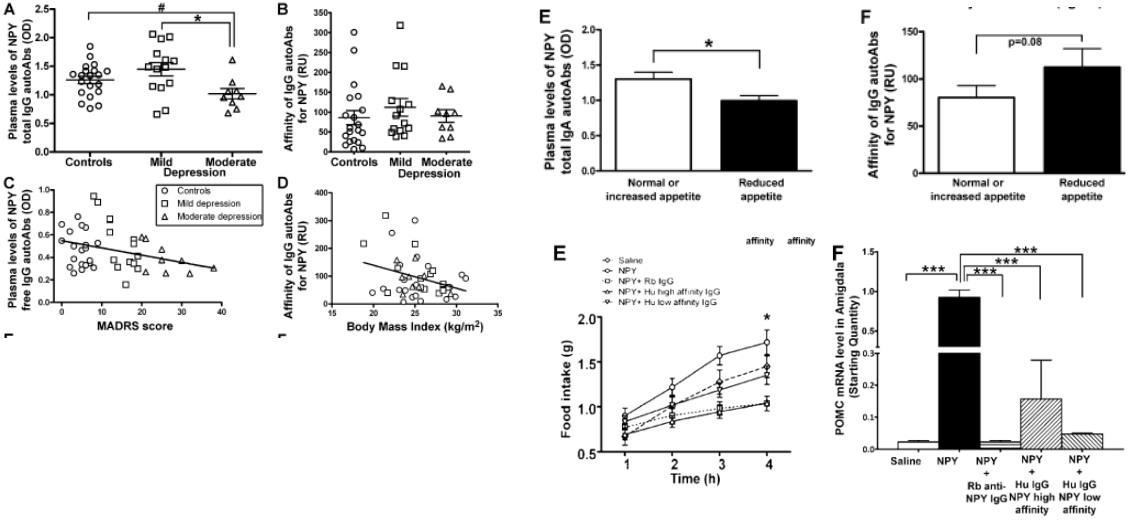
Fig. 5. Immunostaining of magnocellular neurons in the paraventricular (PVN, A–D) and in the supraoptic (SON, E–H) nuclei of the rat hypothalamus by IgG autoAbs from plasma of a patient with moderate depression (green, A,E) as well as by OT (red, B,F) and by VP (purple, C,G) antisera. Figures D and H represent merged images of all three markers. 3v, third ventricle, OC, optic chiasm, scale bars A–D, 200 μm, E–H, 100 μm.

Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 118–125

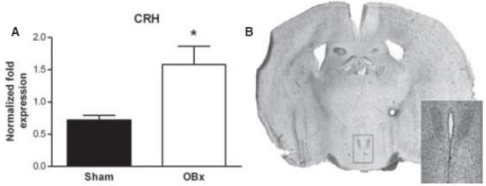
Anti-neuropeptide Y plasma immunoglobulins in relation to mood and appetite in depressive disorder

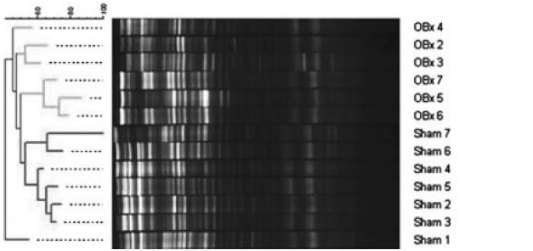
Psychoneuroendocrinology (2012) 37, 1457—1467

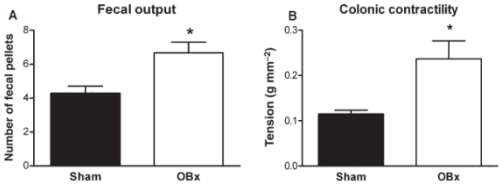
Frederico D. Garcia [a], Quentin Coquerel [a], Jean-Claude do Rego [b], Aurore Cravezic [b], Christine Bole-Feysot [a], Evelyn Kiive [c], Pierre Déchelotte [a], Jaanus Harro [c], Sergueï O. Fetissov [a,*]

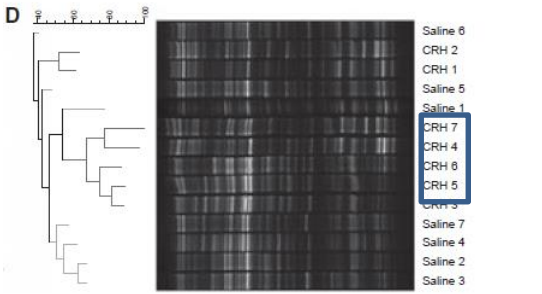


Altered colonic function and microbiota profile in a mouse model of chronic depression



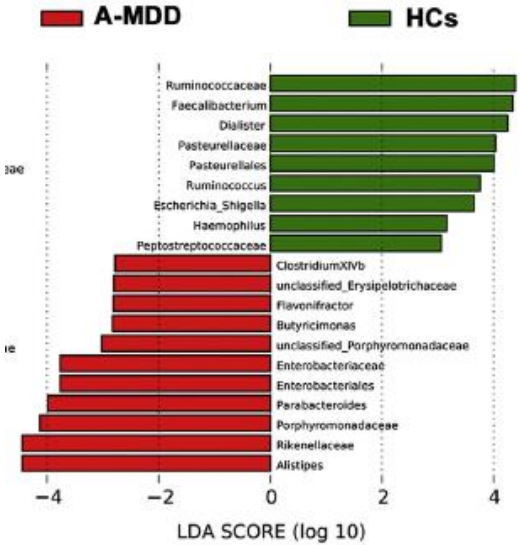






Neurogastroenterol Motil (2013) **25**, 733–e575

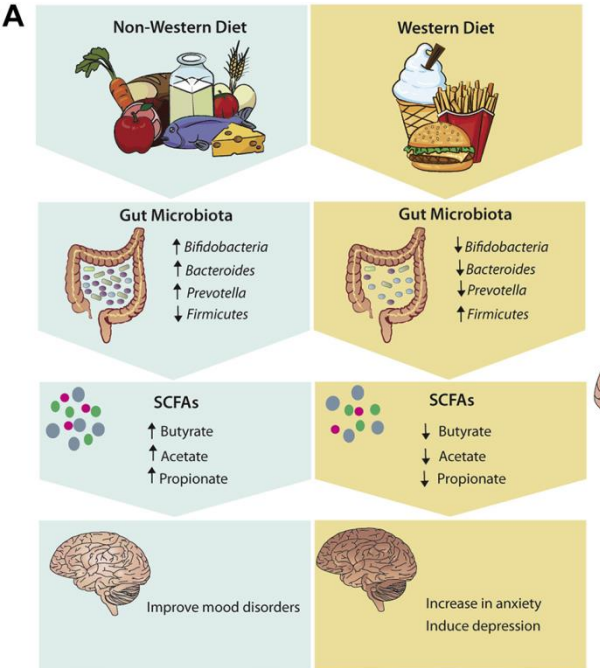
Altered fecal microbiota composition in patients with major depressive disorder

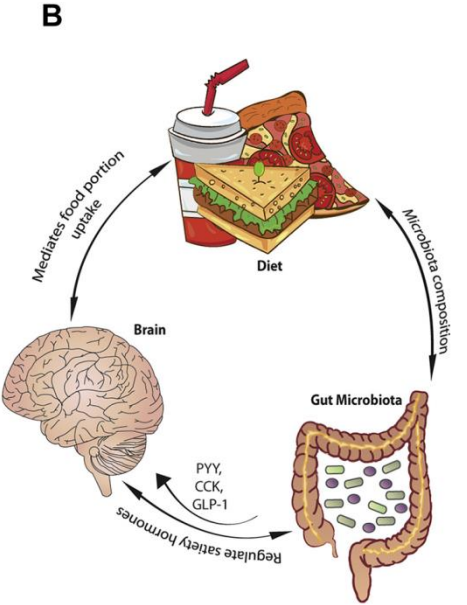


Most notably, the MDD groups had increased levels of Enterobacteriaceae and *Alistipes* but reduced levels of *Faecalibacterium*. A negative correlation was observed between *Faecalibacterium* and the severity of depressive symptoms. These findings enable a better understanding of changes in the fecal microbiota

Jiang Brain Behav Imm 2016c

Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry





Sandhu Transl Res 2017

Psychobiotics: A Novel Class of Psychotropic

Timothy G. Dinan, Catherine Stanton, and John F. Cryan

BIOL PSYCHIATRY 2013;■:■■–■■

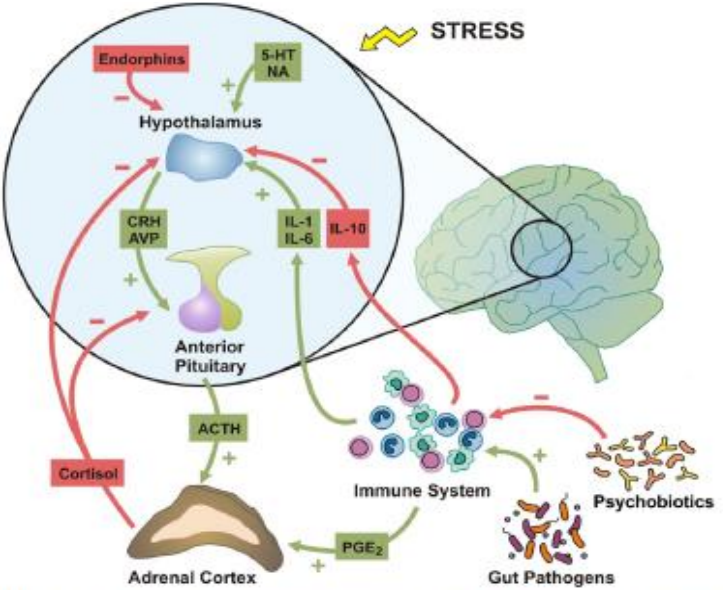
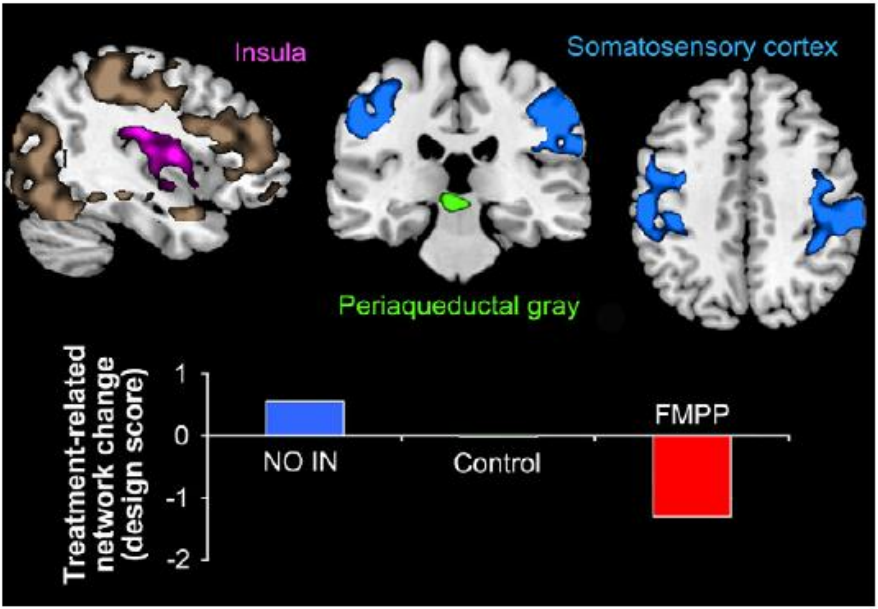


Figure 1. Psychosocial stress is a dominant factor in the genesis of major depression. Stress results in activation of the hypothalamic-pituitary-adrenal axis by bringing about the release of corticotropin releasing hormone (CRH) and vasopressin (AVP) together with altered gut barrier

Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity

KIRSTEN TILLISCH,[1] JENNIFER LABUS,[1] LISA KILPATRICK,[1] ZHIGUO JIANG,[1] JEAN STAINS,[1] BAHAR EBRAT,[1] DENIS GUYONNET,[2] SOPHIE LEGRAIN–RASPAUD,[2] BEATRICE TROTIN,[2] BRUCE NALIBOFF,[1] and EMERAN A. MAYER[1]



Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials

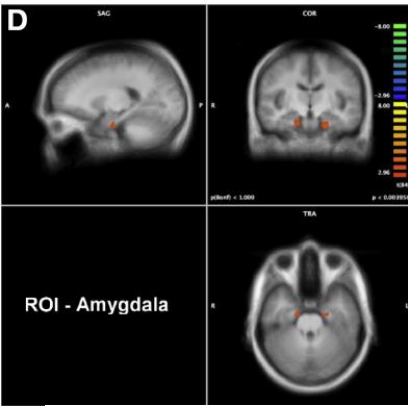
Meysam Pirbaglou[a], Joel Katz[a,b], Russell J. de Souza[c], Jennifer C. Stearns[d], Mehras Motamed[a], Paul Ritvo[a,b,e,*]

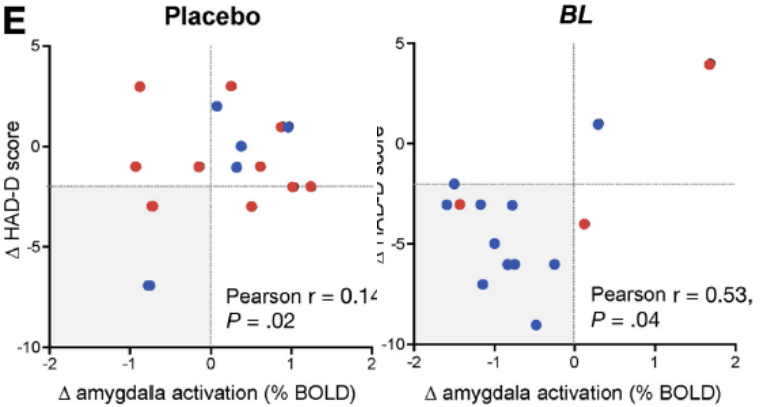
- 10 PRCT
- varied strains, single or combination
- different clinical settings and criteria
- heterogeneity
- globally in favour of intervention
- need for additional studies

NUTRITION RESEARCH 36 (2016) 889–898

Probiotic *Bifidobacterium longum* NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome

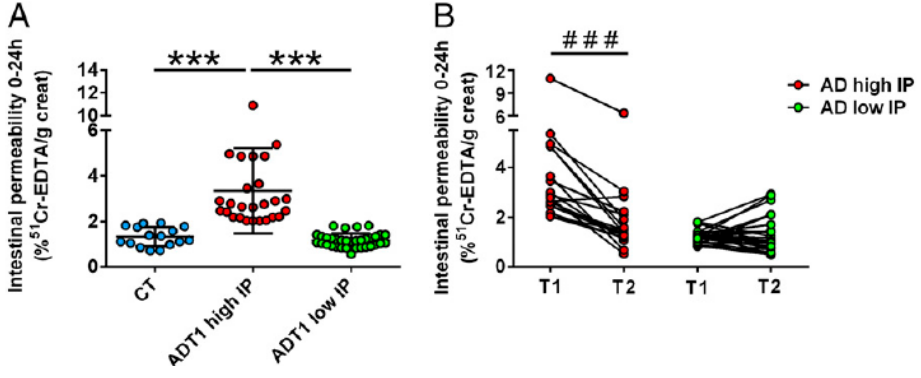
After 6 weeks: 64% improvment of depression score in the BL group vs 32% in the placebo group (p=0.04, ITT)

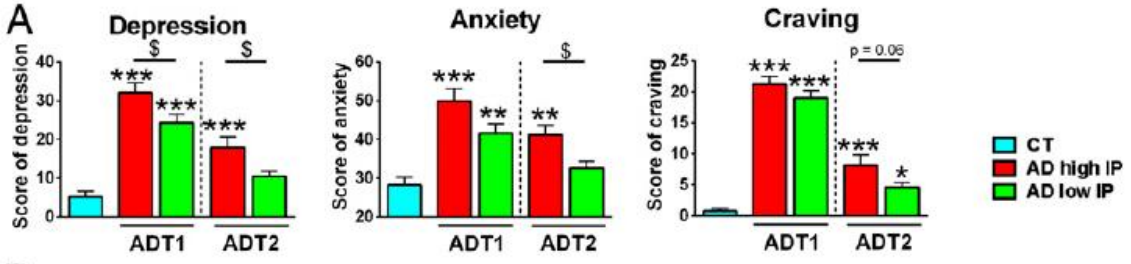




Pinto Sanchez Gastro 2017

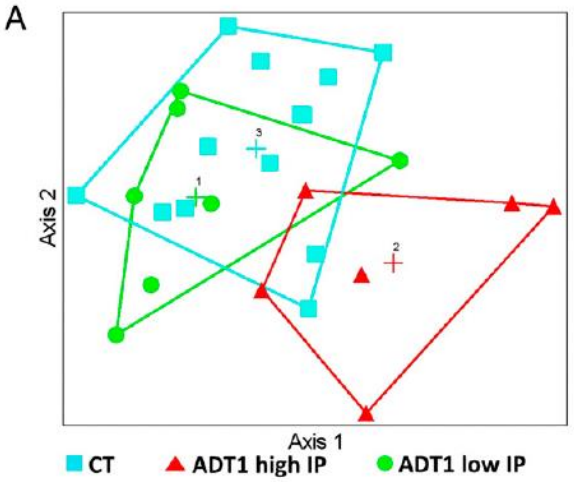
Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity

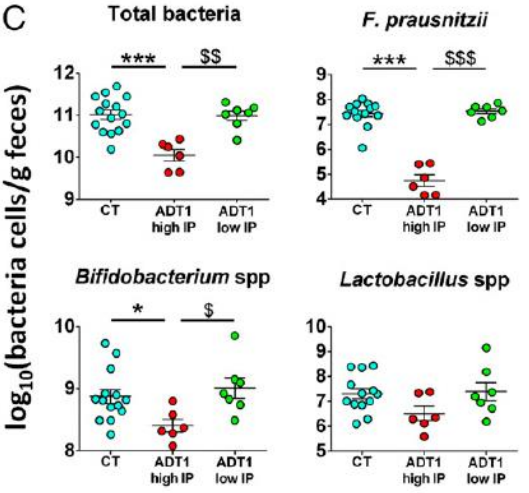




Leclercq et al, PNAS 2014

Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity



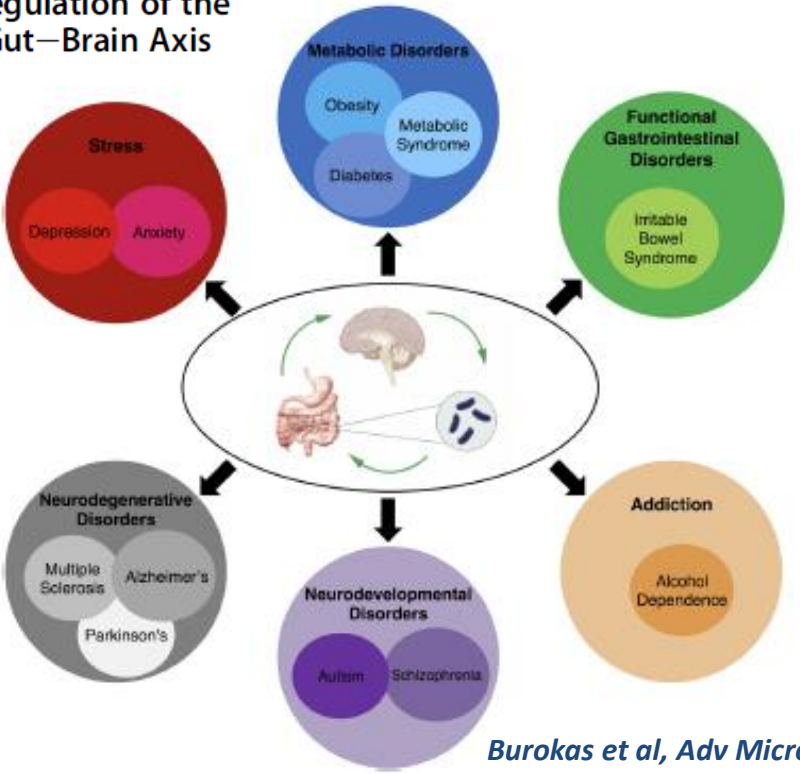


Leclercq et al, PNAS 2014

Relevance of the microbiota-gut-brain axis

- The microbiota-gut-brain axis
- Weight and eating behaviour
- Digestive diseases : IBD, IBS, Coeliac
- Neuropsychiatric disorders
- **Perspectives and challenges**

Microbiota Regulation of the Mammalian Gut–Brain Axis



Burokas et al, Adv Microb Rev 2015

Anticancer effects of the microbiome and its products

Laurence Zitvogel[1–4], Romain Daillère[1–3], María Paula Roberti[1–3], Bertrand Routy[1–3] and Guido Kroemer[4–10]

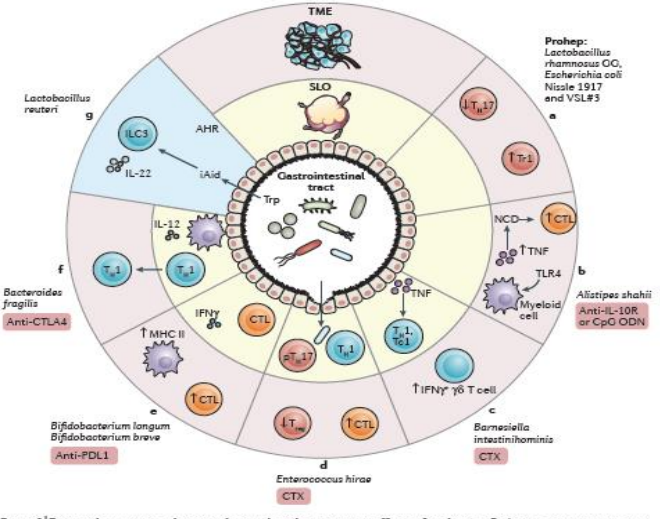
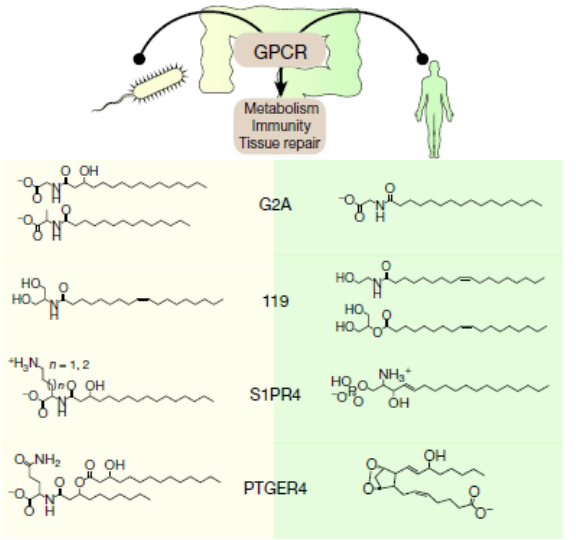


Figure 2 | **Potential immune mechanisms that explain the anticancer effects of probiotics.** Probiotic microorganisms may

Commensal bacteria make GPCR ligands that mimic human signalling molecules



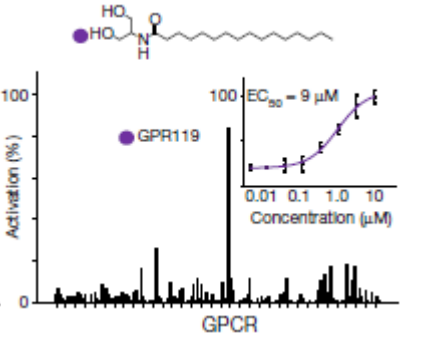
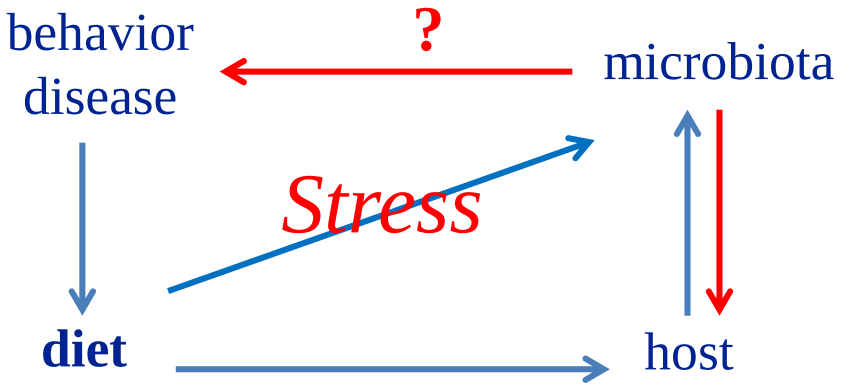


Figure 4 | Structural mimicry of GPCR ligands. Comparison of microbiota-encoded and human GPCR ligands suggests structural and functional complementarity.

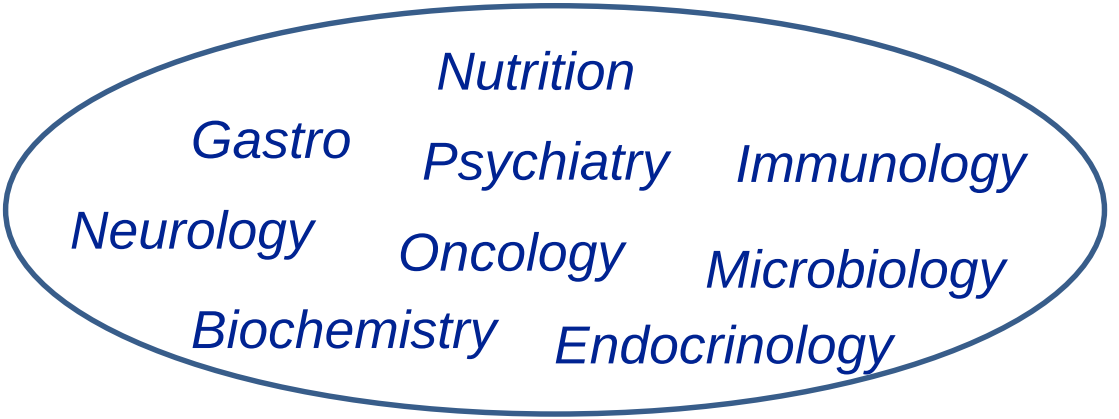
Cohen et al, Nature 2017

Scanning bugs: the new crystal ball ?

Diet and stress as parents, the disease as the egg ?



Gut-brain axis : an area for integrative medicine and translational research



Innovative concepts → intellectual property → added economical value

Thanks to UMR 1073 – Nutrition et dysfonction de l'axe intestin-cerveau

Thank you for your attention – Enjoy Rouen Normandie!