学術シンポジウム「乳幼児の食に迫る：発達保育実践政策学の根幹」.
2020年2月1日, 東京

腸内細菌と脳腸相関

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九州大学

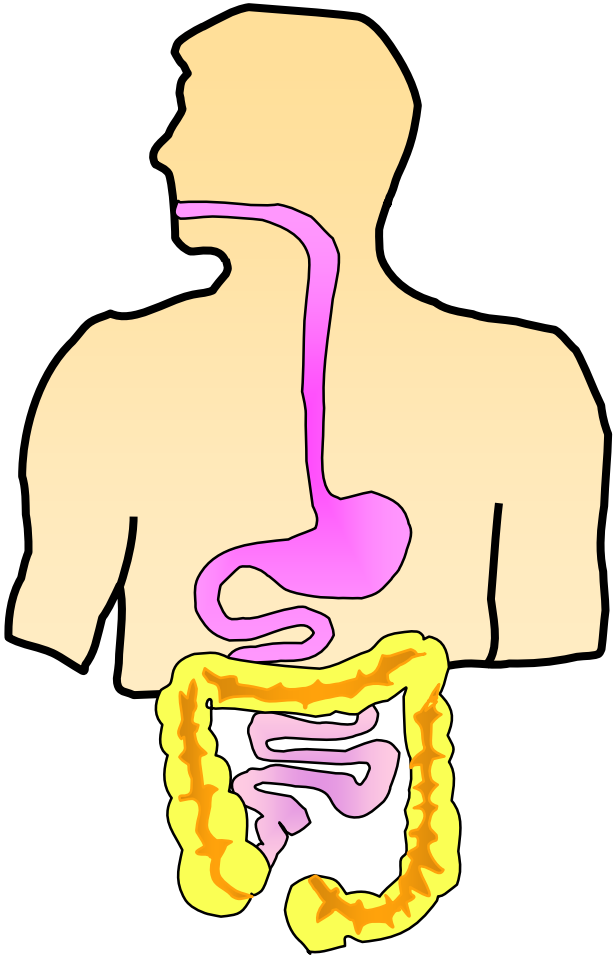
ヒト腸内細菌叢

(Berg, 1996)

口腔
(200 species)

胃
(Helicobacter pylori)

回腸
(10^8 bacteria)

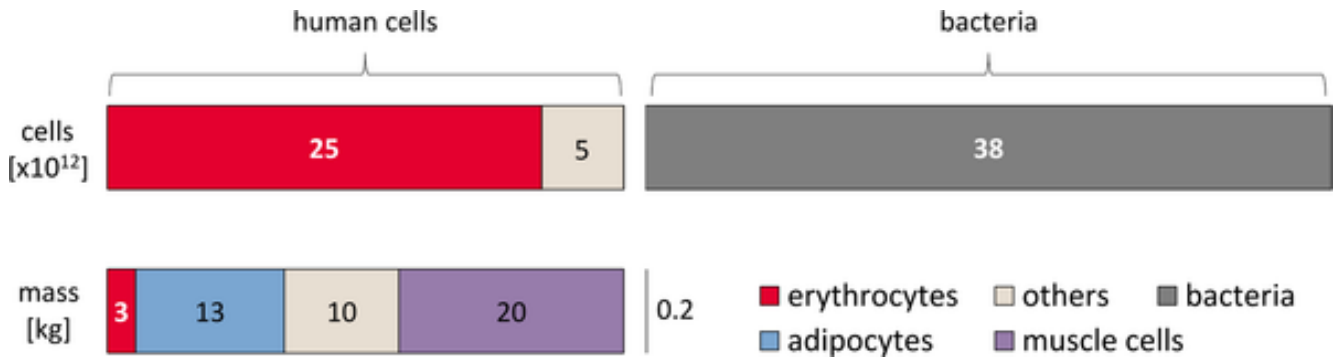


大腸
(10^{10}-10^{11})

400-500species:
Bacteroides
Peptostreptococcus
Eubacterium
Bifidobacterium
Ruminococcus
Bacillus
Fusobacterium
Clostridium
Lactobacillus
Enterococcus
Enterobacter

腸内細菌数 > 体細胞数

Fig 3. Distribution of cell number and mass for different cell types in the human body (for a 70 kg adult man).



Sender R, Fuchs S, Milo R (2016) Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLOS Biology 14(8): e1002533. https://doi.org/10.1371/journal.pbio.1002533
https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002533

Development of gut microbiota in humans

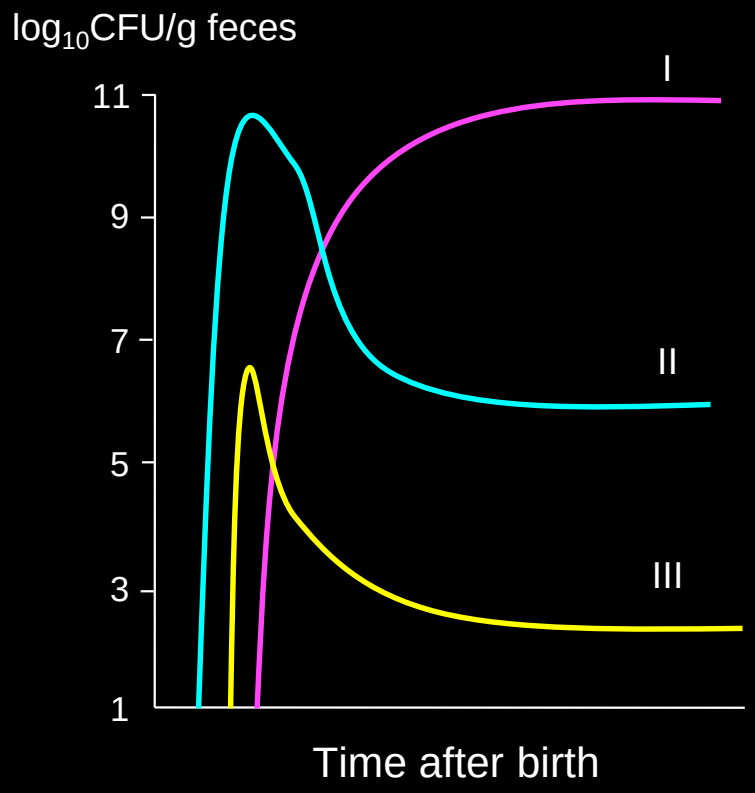
(Mitsuoka & Hayakawa, 1972)

Kinetics of colonization

Intestinal flora

Counts

Species



Symbiotic

10^9~10^{11} I
- *Bacteroides*
- *Eubacterium*
- *Bifidobacterium*
- *Peptostreptococcus*

10^5~10^8 II
- *Lactobacillus*
- *E. coli*
- *Streptococcus*
- *Veillonella*

0~10^4 III
- *Clostridium perfringens*
- *Bacteroides*
- *Pseudomonas aeruginosa*
- *Proteus*
- *Staphylococcus aureus*

Pathogenic

腸内フローラの生理的意義

物質代謝の調節：

最近では、新たな生理作用や疾患（肥満、アレルギー、精神疾患など）との関係が注目されている

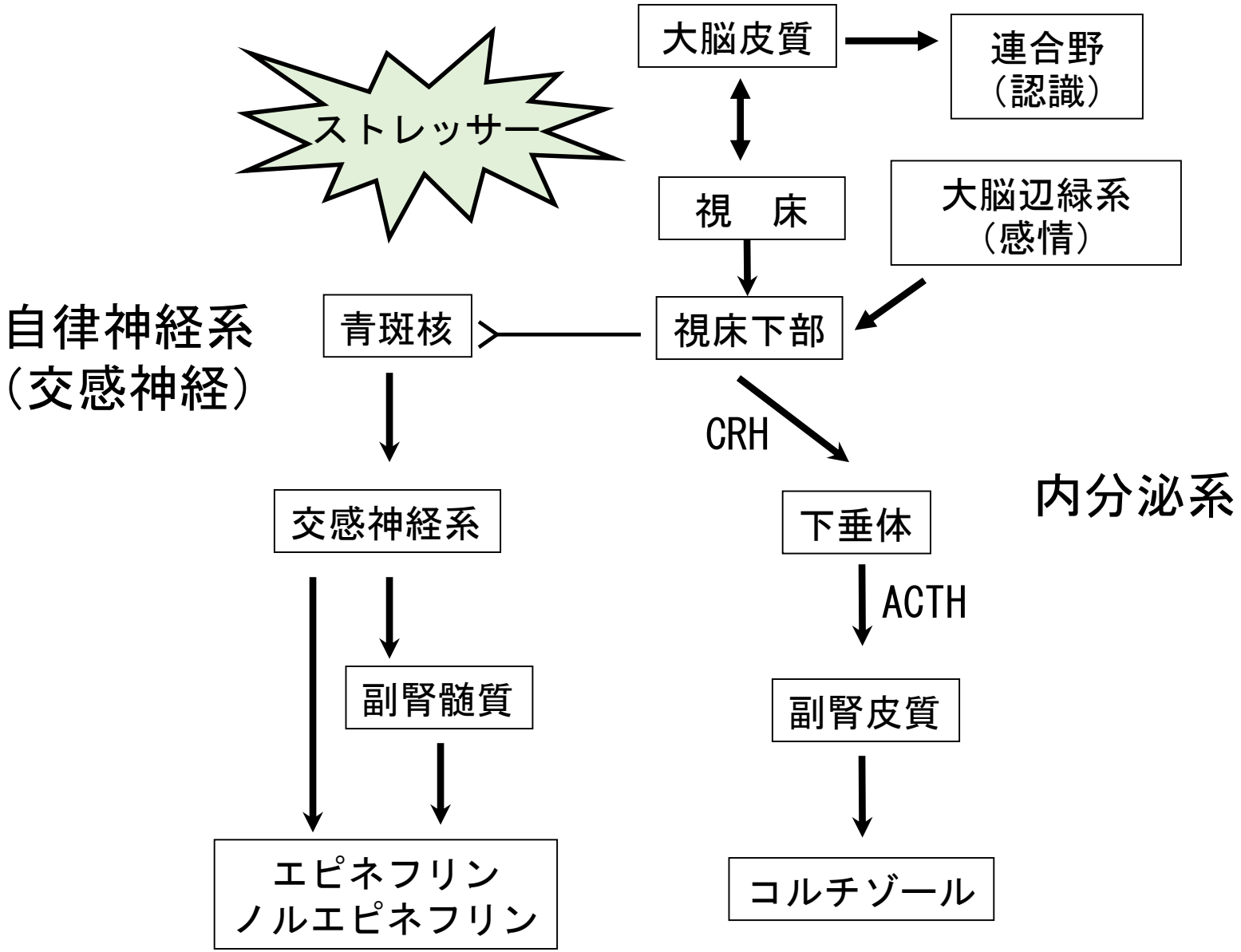
蠕動運動・消化吸収の促進

感染防御

粘膜免疫組織の発達

腸内細菌によるストレス応答・行動特性の制御

ストレス時における交感神経系および視床下部-下垂体-副腎軸の活性化



Modulation of HPA axis response by early-life environments

Manipulation	HPA response at adults	References
Handling	↓	*Science 239;766, 1988*
Maternal deprivation	early ↑	*Dev Psychobiology 24;547, 1992*
	late ↓	*Dev Brain Res 111;245, 1998*
Social isolation	↓	*Endocrinology 139;579, 1988*
Maternal care	↓	*Science 277;1659, 1997*

↑ Increase in HPA response at adults

↓ Decrease in HPA response at adults

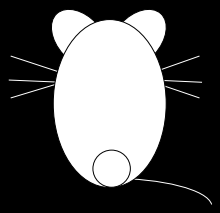
Can gut microbiota affect HPA stress response?

We examined HPA reaction to restraint stress by comparing the three groups of mice:

1. **Germ-free (GF)** mice that had no microorganisms
2. **Specific pathogen-free (SPF)** mice raised with a normal microbiota but not with specific pathogen
3. **Gnotobiotic mice** raised with a single strain of bacterium

Materials & Methods

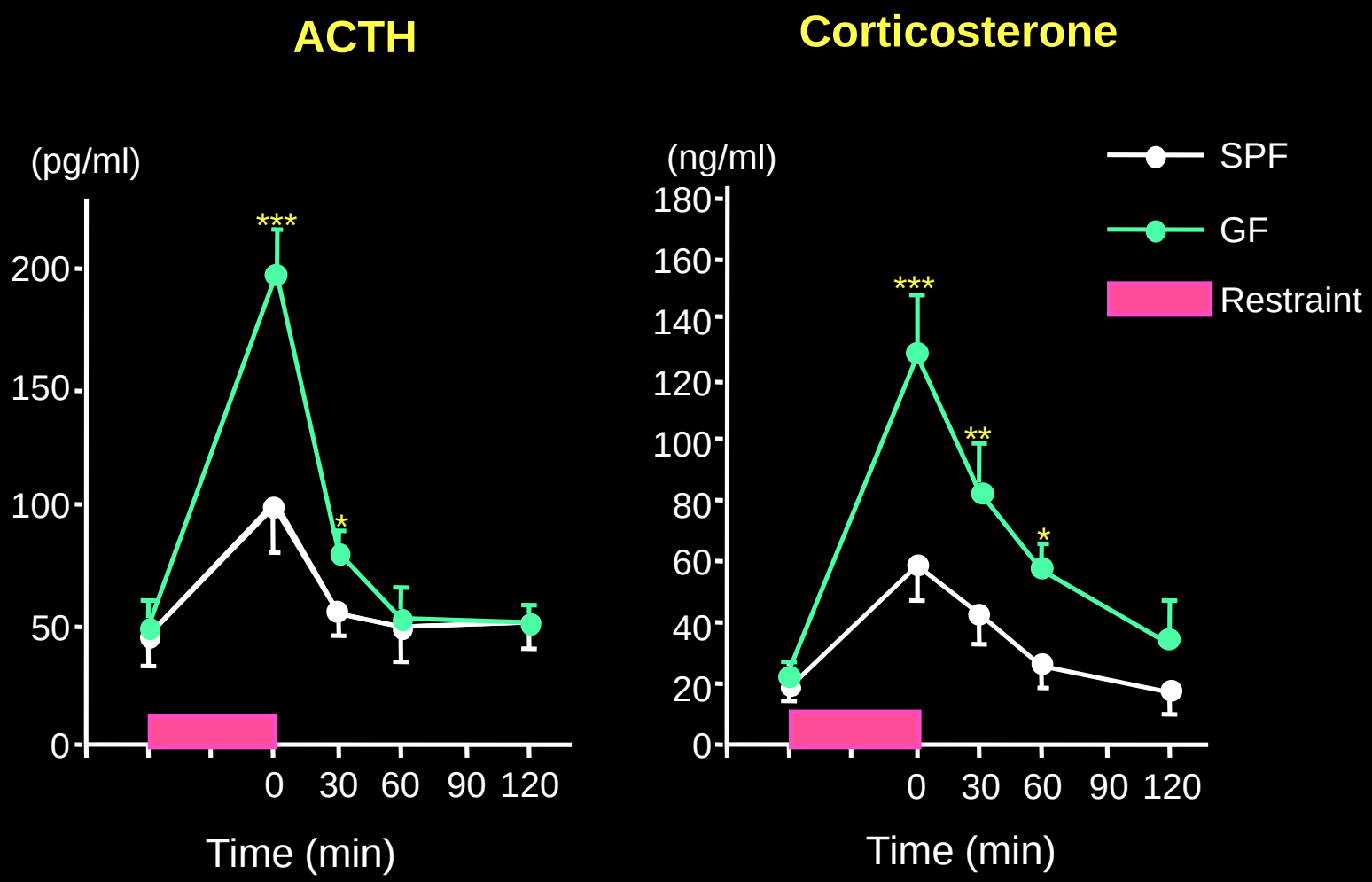
: 1 hr-restraint using a 50-ml conical tube



SPF or GF
BALB/c mouse
♂ 9 wks

Peripheral blood: Measurement of plasma ACTH and corticosterone levels in response to 1-hr restraint

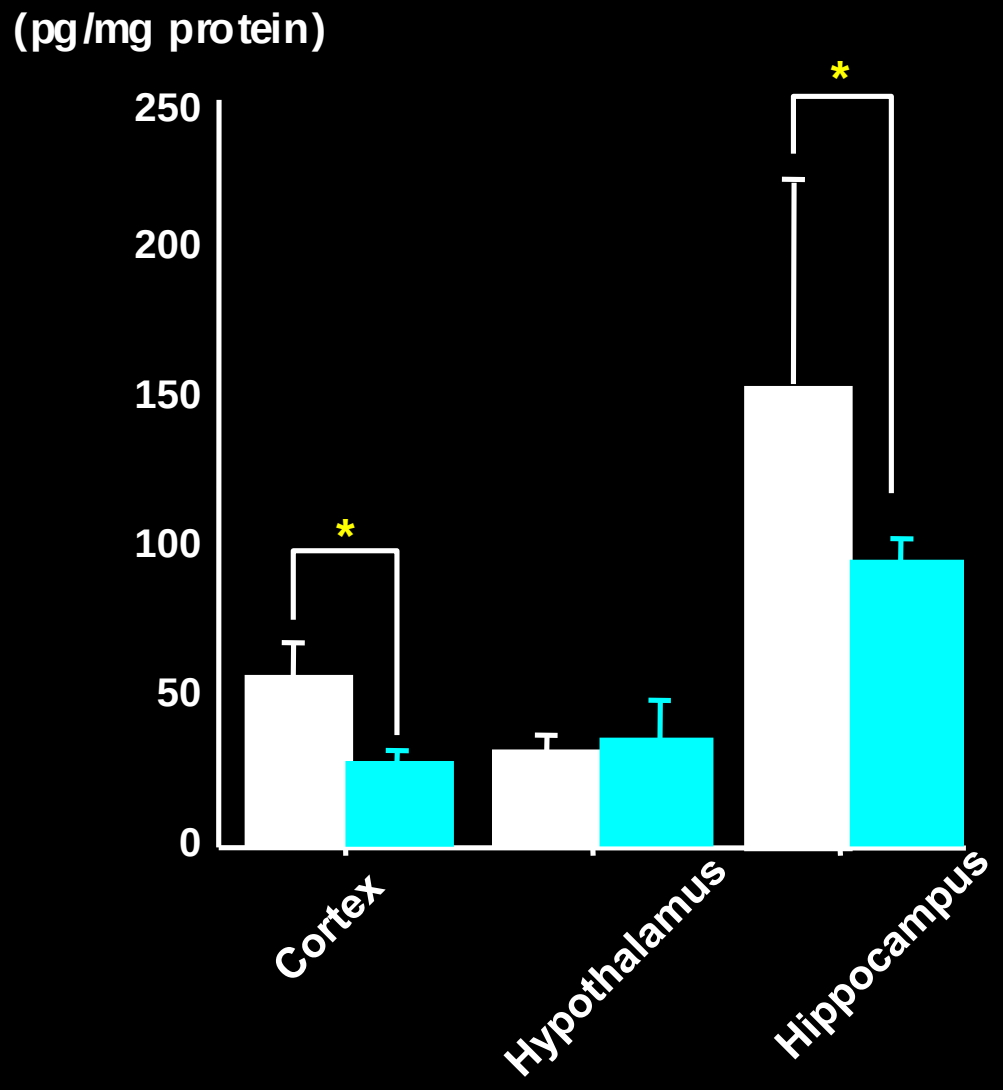
Plasma ACTH and corticosterone responses following restraint stress are higher in GF mice than in SPF mice



(Sudo N. 2004)

**** P < 0.001, ** P < 0.01, * P < 0.05*

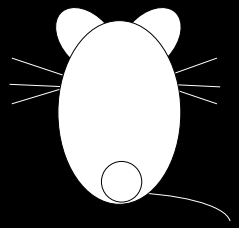
BDNF concentrations



* *P < 0.05*

(Sudo N. 2004)

Materials & Methods



BALB/c
♂ 9 wks

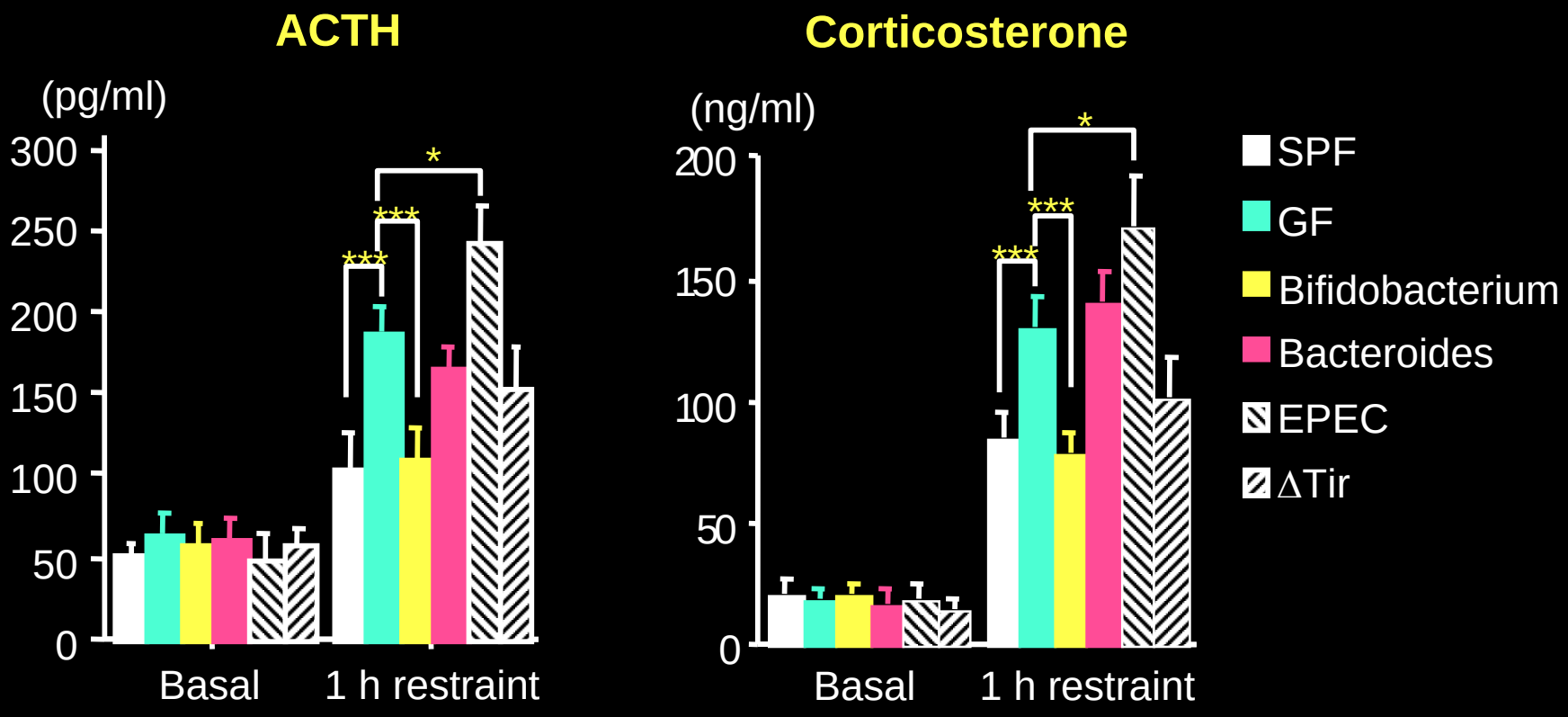
1) SPF
2) GF
3) Gnotobiotic

- *Bifidobacterium infantis*
- *Bacteroides vulgatus*
- *Enteropathogenic E-coli* (EPEC)
- EPEC mutant ΔTir

Peripheral blood: Measurement of plasma ACTH and corticosterone levels before and after 1 hr-restraint.

Brain: Measurement of CRF, GR and BDNF levels in various regions of the brain

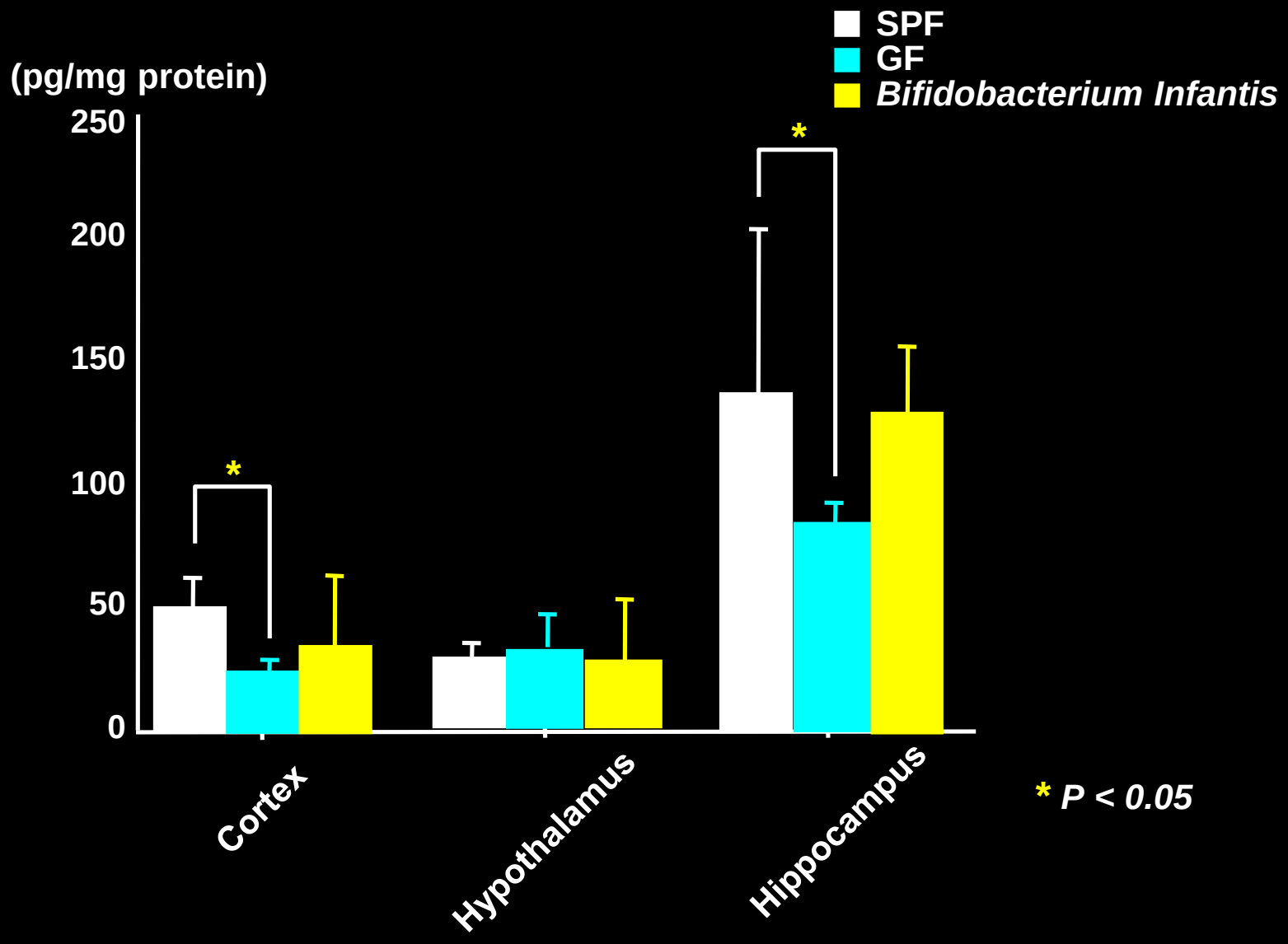
Restraint stress-induced ACTH and corticosterone elevation in gnotobiotic mice



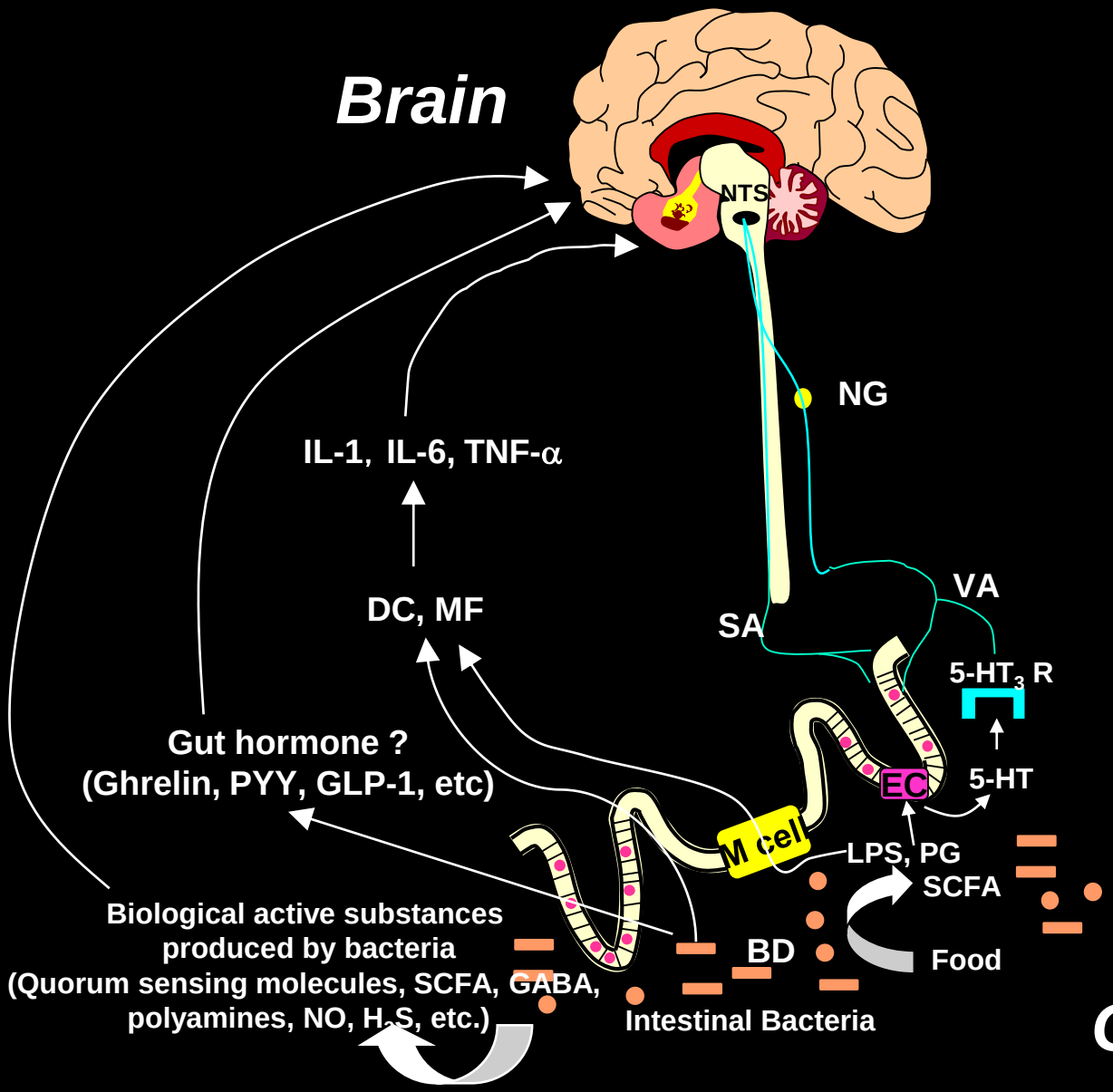
*** P < 0.001, ** P < 0.01, * P < 0.05

(Sudo N. 2004)

BDNF concentrations



Signaling from gut microbes to the brain



BD: bacterial DNA
DC: dendritic cell
EC: enterochromaffin cell
GABA: γ-aminobutyric acid
H2S: Hydrogen sulfide
5-HT: 5-hydroxytryptamine
5-HT3 R: 5-HT type 3 receptor
LPS: lipopolysaccharide
MF: macrophage
NTS: nucleus tractus solitaris
NG: nodose ganglia
NO: nitric oxide
PG: peptidoglycan
SA: spinal afferent nerve
SCFA: short-chain fatty acid
VA: vagal afferent nerve

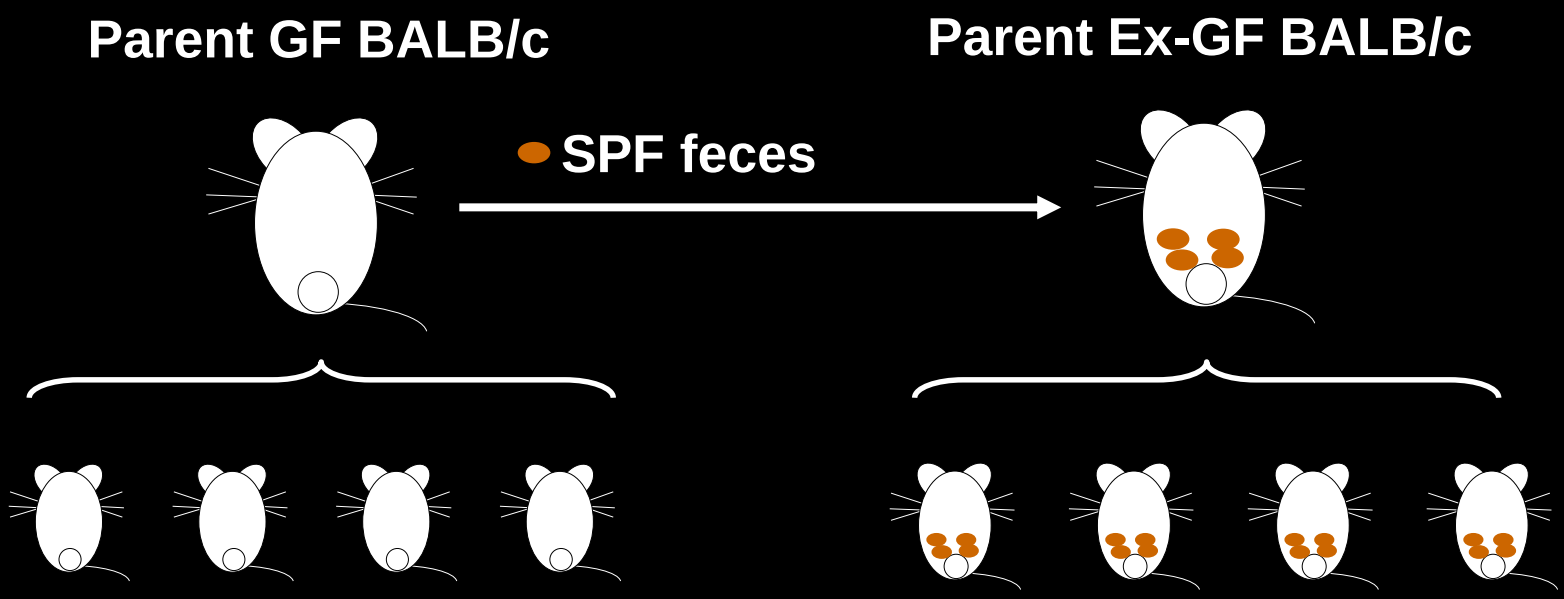
Questions for future research

1.行動面への影響は?

2.メカニズムは?

3.ヒトでは?

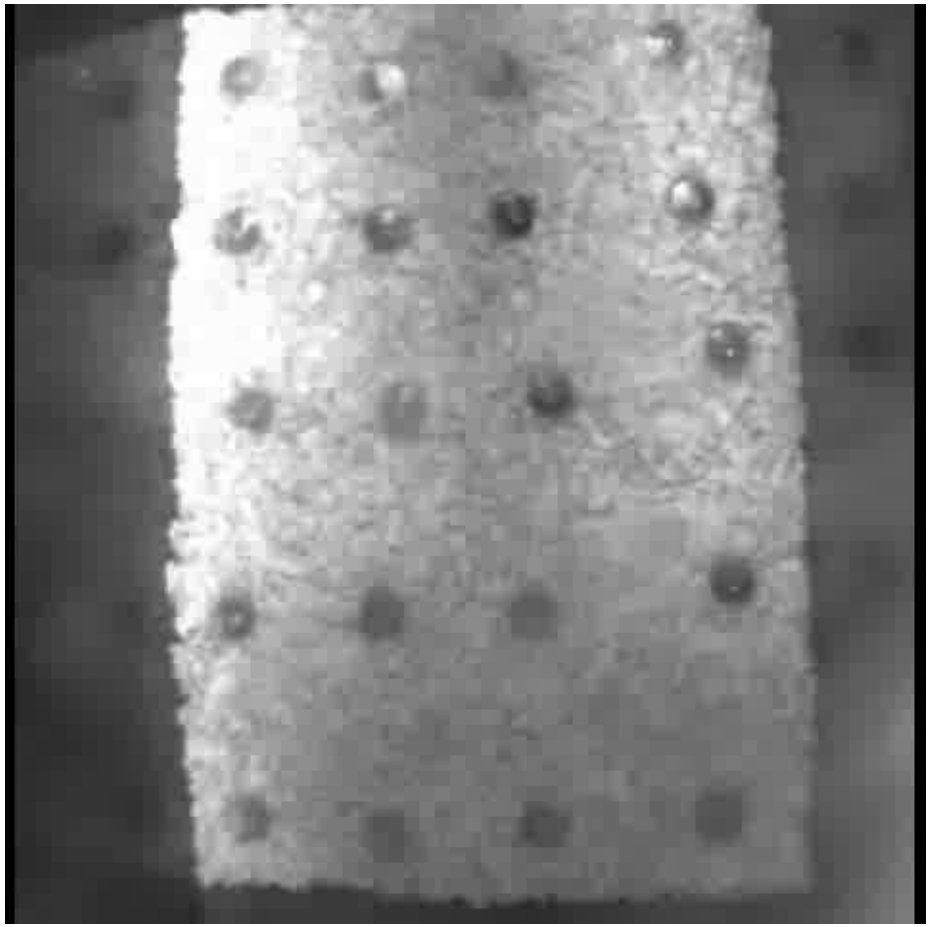
Methods



Behavioral analysis under contamination-free environment

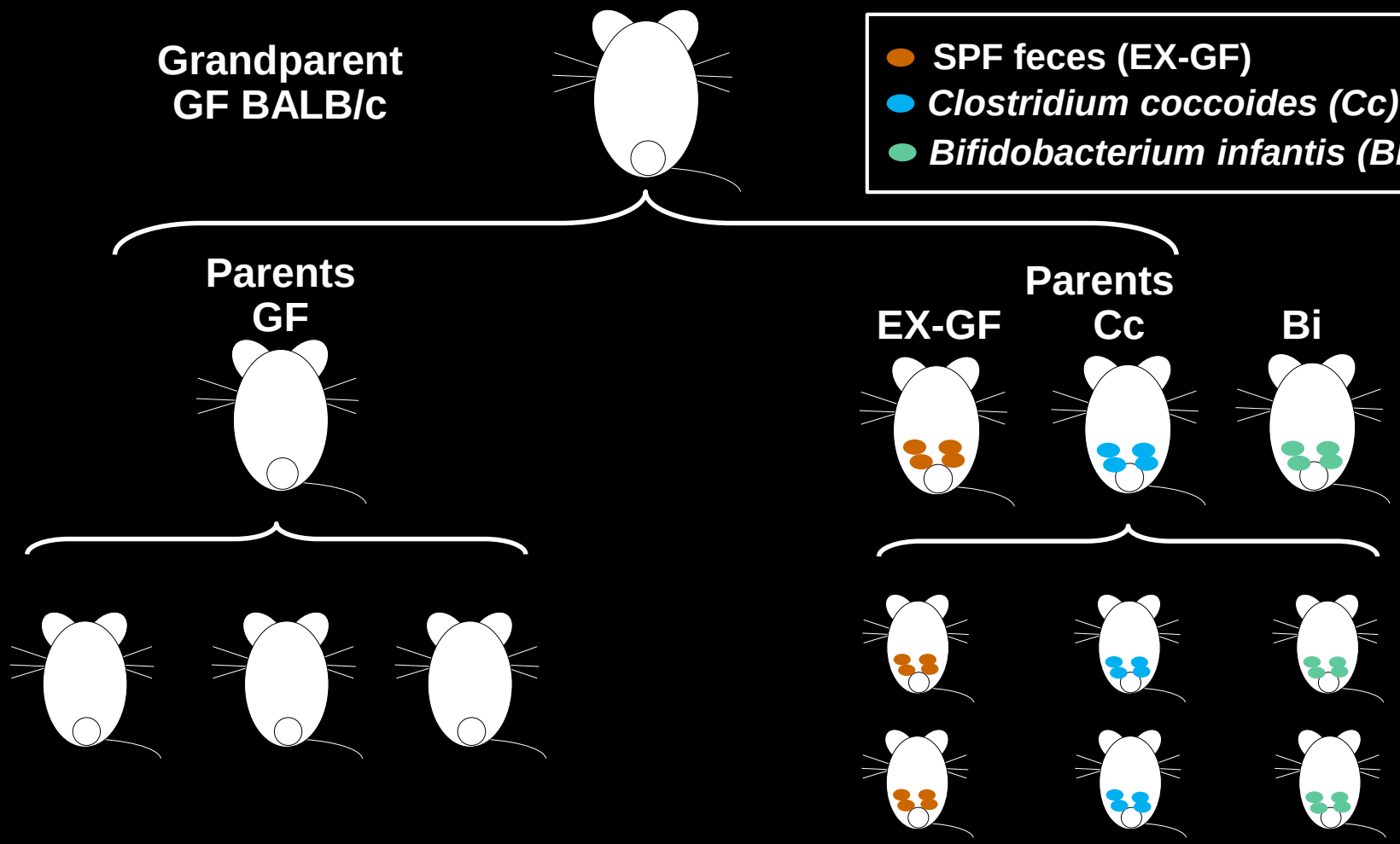
- open field test（locomotor, anxiety）
- Marble-burying test（anxiety）

Marble burying behavior of GF mouse



GF mice buried twice as many marbles as SPF mice

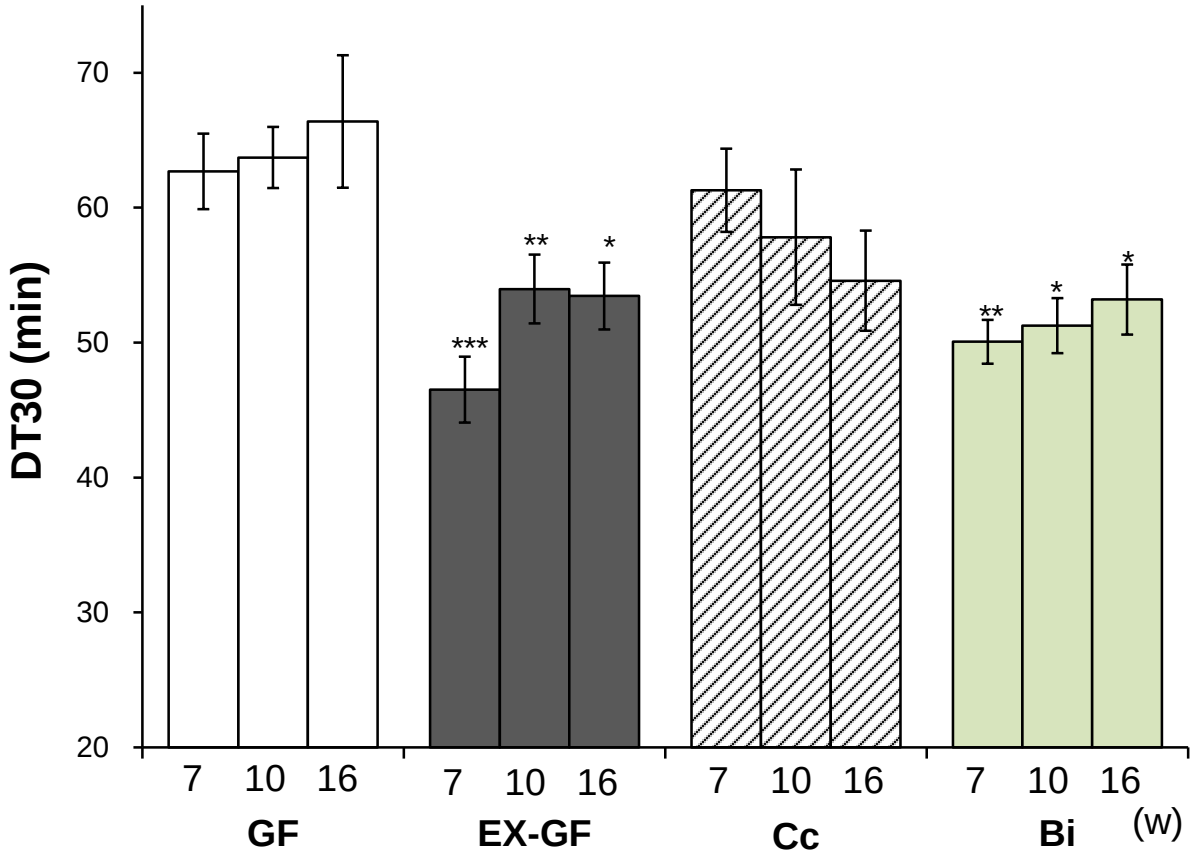
Gnotobiotic mice for behavioral experiments



Behavioral analysis under contamination-free environment

- open field test（locomotor, anxiety）
- Marble-burying test（anxiety）

Locomotor activity evaluated by open-field test

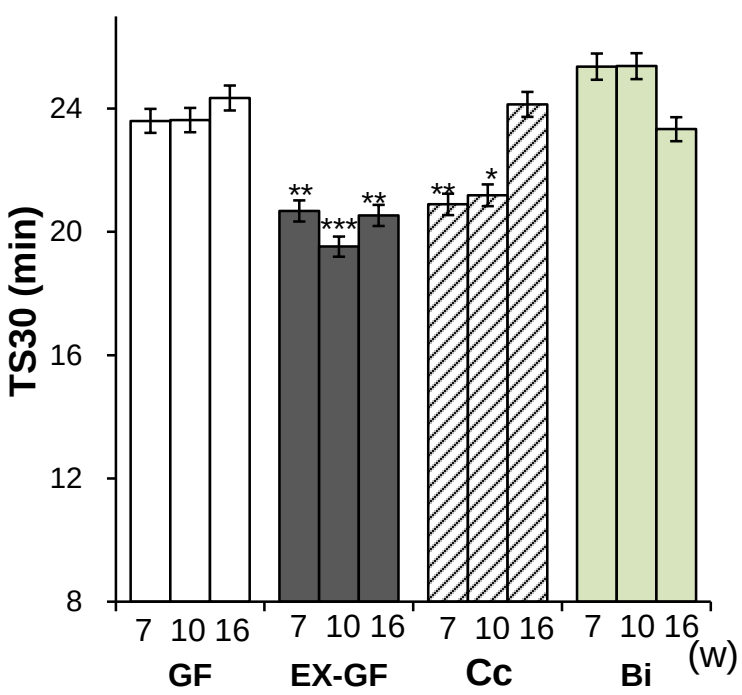


Administration with SPF feces (EX-GF) or *Bifidobacterium infantis* renders GF mice less active

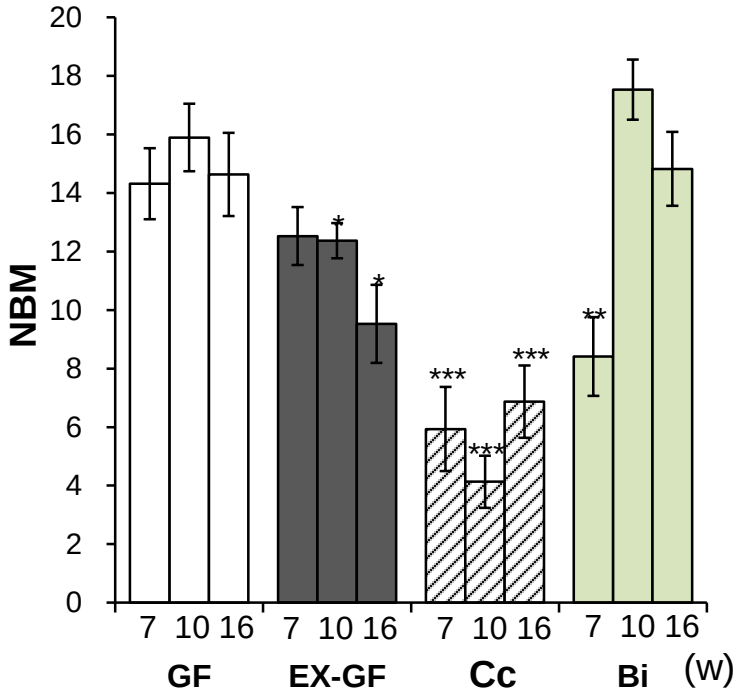
(Nishino, 2013)

Anxiety-related behavior

Open-field test



Marble-burying test



Colonization of SPF flora or *Clostridium coccoides* makes GF mice less anxious

(Nishino, 2013)

Behaviors alter microbiomes.

Behaviors impact microbiomes

Animal	Microbial species or consortium	Interaction with behavior	Implication
 Kudzu bug (*Megacopta cribraria*)	*Ishikawaella capsulata*	When born, bugs feed on capsules of symbionts; if no capsules are present, nymphs wander in search of microbes	Behaviors shape symbiont acquisition
 Green iguana (*Iguana iguana*)	Gut microbiota	Juvenile iguanas eat soil or feces to tailor the microbiota to their current diet	Animals may adjust the microbiota at different life-history stages
 Bobtail squid (*Euprymna scolopes*)	*Vibrio fischeri*	Squids eject bioluminescent bacteria daily	Suggests animals can actively control their symbiont populations

Vanessa O. Ezenwa et al. Science 2012;338:198-199

Microbiomes alter behaviors.

Microbiomes impact behaviors

Animal	Microbial species or consortium	Interaction with behavior	Implication
 Fruit fly (*Drosophila melanogaster*)	Gut microbiota	Diet-specific microbiota influence mating preferences	Microbes could drive speciation
 Mosquito (*Anopheles gambiae*)	Human skin microbiota	Skin microbes of humans influence attraction to mosquitoes	Differential attraction could impact disease spread
 Mouse (*Mus musculus*)	*Lactobacillus rhamnosus*	The probiotic *L. rhamnosus* decreases anxiety in mice	Suggests bacteria can alter mood

Vanessa O. Ezenwa et al. Science 2012;338:198-199

PNAS

Commensal bacteria play a role in mating preference of *Drosophila melanogaster*

Gil Sharon[a], Daniel Segal[a], John M. Ringo[b], Abraham Hefetz[c], Ilana Zilber-Rosenberg[d], and Eugene Rosenberg[a,1]

[a]Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv 69978, Israel; [b]School of Biology and Ecology, University of Maine, Orono, ME 04469; [c]Department of Zoology, Tel Aviv University, Tel Aviv 69978, Israel; and [d]18 Rachavat Ilan St., Givat Shmuel 51905, Israel

Edited by R. John Collier, Harvard Medical School, Boston, MA, and approved September 28, 2010 (received for review July 12, 2010)

Development of mating preference is considered to be an early event in speciation. In this study, mating preference was achieved by dividing a population of *Drosophila melanogaster* and rearing one part on a molasses medium and the other on a starch medium. When the isolated populations were mixed, "molasses flies" preferred to mate with other molasses flies and "starch flies" preferred to mate with other starch flies. The mating preference appeared after only one generation and was maintained for at least 37 generations. Antibiotic treatment abolished mating preference, suggesting that the fly microbiota was responsible for the phenomenon. This was confirmed by infection experiments with microbiota obtained from the fly media (before antibiotic treatment) as well as with a mixed culture of *Lactobacillus* species and a pure culture of *Lactobacillus plantarum* isolated from starch flies. Analytical data suggest that symbiotic bacteria can influence mating preference by changing the levels of cuticular hydrocarbon sex pheromones. The results are discussed within the framework of the hologenome theory of evolution.

identification. Several replicates of each experiment were performed with the wing clippings alternating between populations (i.e., half of each experiment was done with wing clipping of flies from one treatment, and the other half was the reciprocal). Even though wing clipping has been previously shown not to affect mating preference in *Drosophila* (9, 10), we used a counterbalanced design for mating preference tests to control for any possible wing clipping effects.

In the first experiment, the mating preference test was performed after 11 generations (Fig. 1*B*). Of the 38 recorded matings, 29 were homogamic, i.e., "starch males" with "starch females" and "CMY males" with "CMY females," whereas only nine were heterogamic (i.e., "starch" × "CMY"). These results demonstrate a significant positive sexual isolation index (SII) (11): SII = 0.53 ± 0.14 (SEM) and $P = 0.0012$ (binomial test), with the following assumptions:

（Sharon et al., 2010）

ショウジョウバエでは、ある集団を2つに分けて数世代を別々のエサで飼うと、両者を再び混ぜ合わせても同じエサを摂取した雌雄同士が交配する。一方を糖蜜で、もう一方をデンプンで飼うと、その後混ぜ合わせても糖蜜ハエ同士、デンプンハエ同士で交配するが、ハエを抗生物質処理するとその選り好みは消失。この現象には、*Lactobacillus plantarum*によるcuticular hydrocarbon sex pheromone（体表炭化水素性フェロモン）レベルの変動が関与。

Questions for future research

1.行動面への影響は?

2.メカニズムは?

3.ヒトでは?

短鎖脂肪酸
（short chain fatty acids）

脂肪酸の一種であり、炭素の数が6個以下のものを指す。酢酸、プロピオン酸、酪酸などが含まれる。SCFAは、ヒトの大腸において、消化されにくい食物繊維やオリゴ糖を腸内細菌が発酵することにより生成される

―ヤクルト中央研究所ホームページより

ミクログリアの活性化

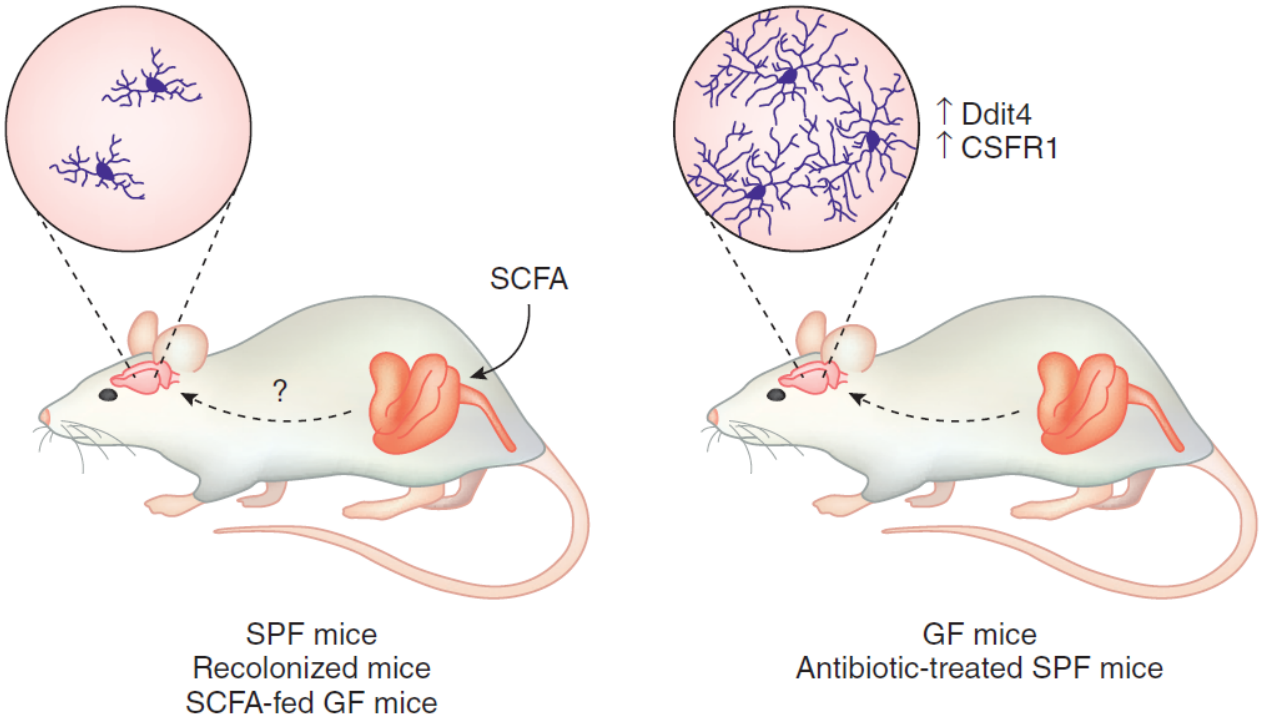


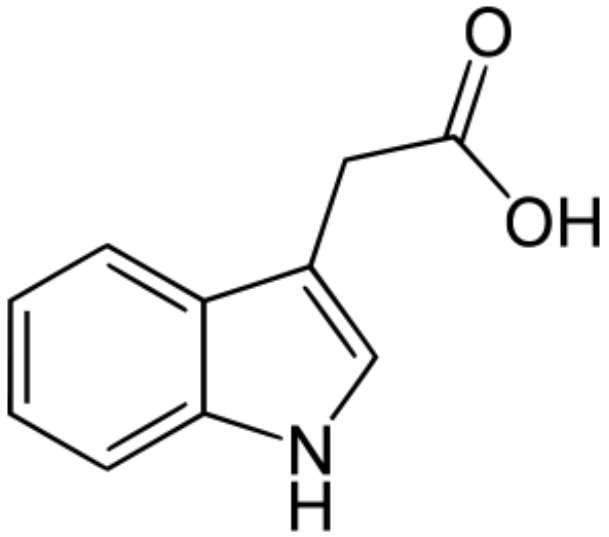
Figure 1 Communication from gut to brain regulates microglia. The typical morphology, territorial boundaries and molecular profile of microglia observed in mice living in standard, clean housing conditions (SPF; left) are changed in mice living in a GF environment (right). Microglia of GF mice display extended processes that encroach on each other's territories and a gene expression profile more akin to that of immature cells (for example, upregulation of CSFR1 and Ddit4). Partial ablation of gut microbiota with antibiotics produces a microglial phenotype similar to the one observed in GF mice, while recolonization of GF mice or feeding with SCFA normalizes the microglial phenotype. GF, germ free; SPF, specific pathogen free; SCFA, short-chain fatty acids.

Nature Neurosci. 2015 Jun 25;18(7):930-1.

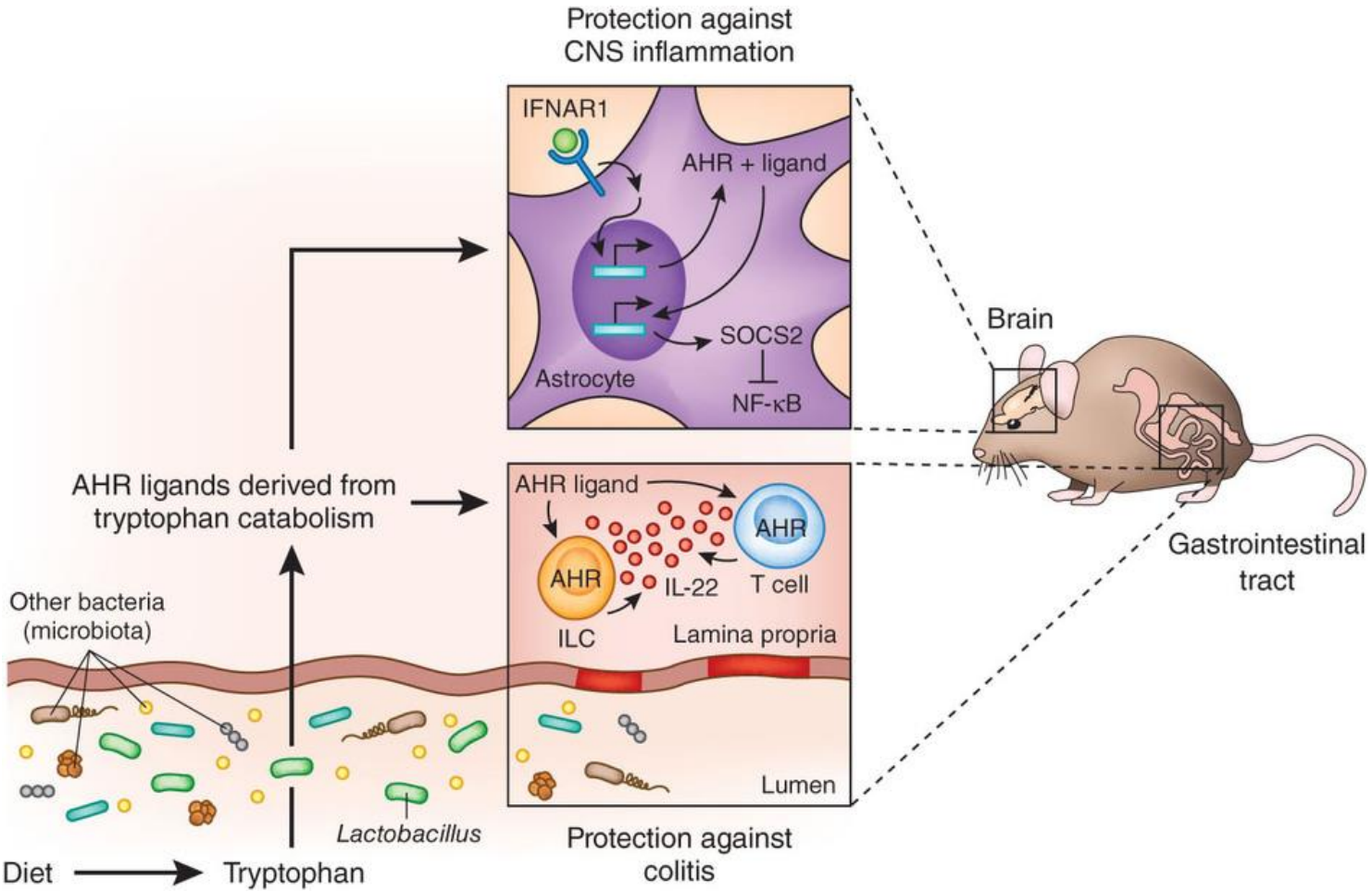
トリプトファン代謝物（インドール類）

腸内細菌や真菌によりトリプトファンから合成される indole-3-acetic acid, indoxyl-3-sulfate, indole-3-propionic acid, indole-3-aldehydeなど。aryl hydrocarbon receptor (AHR) に対するリガンドとして作用する

indole-3-acetic acid



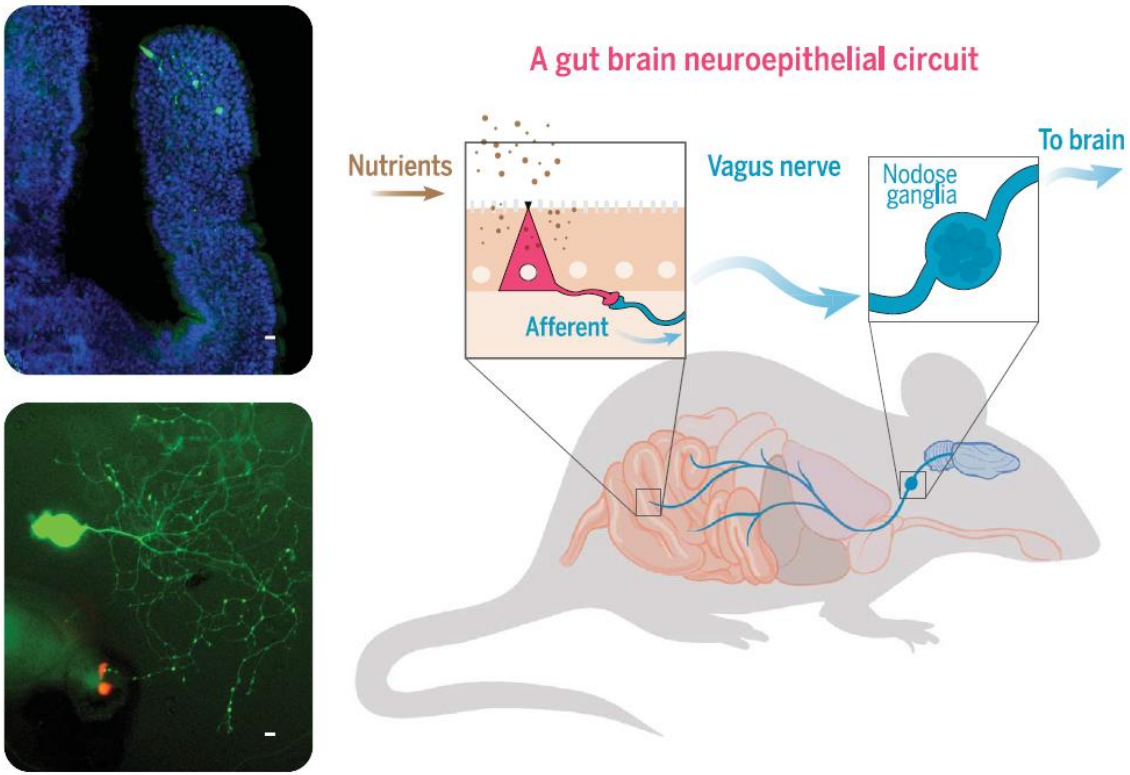
アストロサイトの活性化



Bacteria in the gut catabolize tryptophan into a range of indole derivatives (such as indole-3-acetic acid, indoxyl-3-sulfate, indole-3-propionic acid and indole-3-aldehyde) that are ligands for the aryl hydrocarbon receptor (AHR)

Nature Medicine 22, 581–583 (2016)

最近のトピックス：求心性迷走神経（vagus afferent）



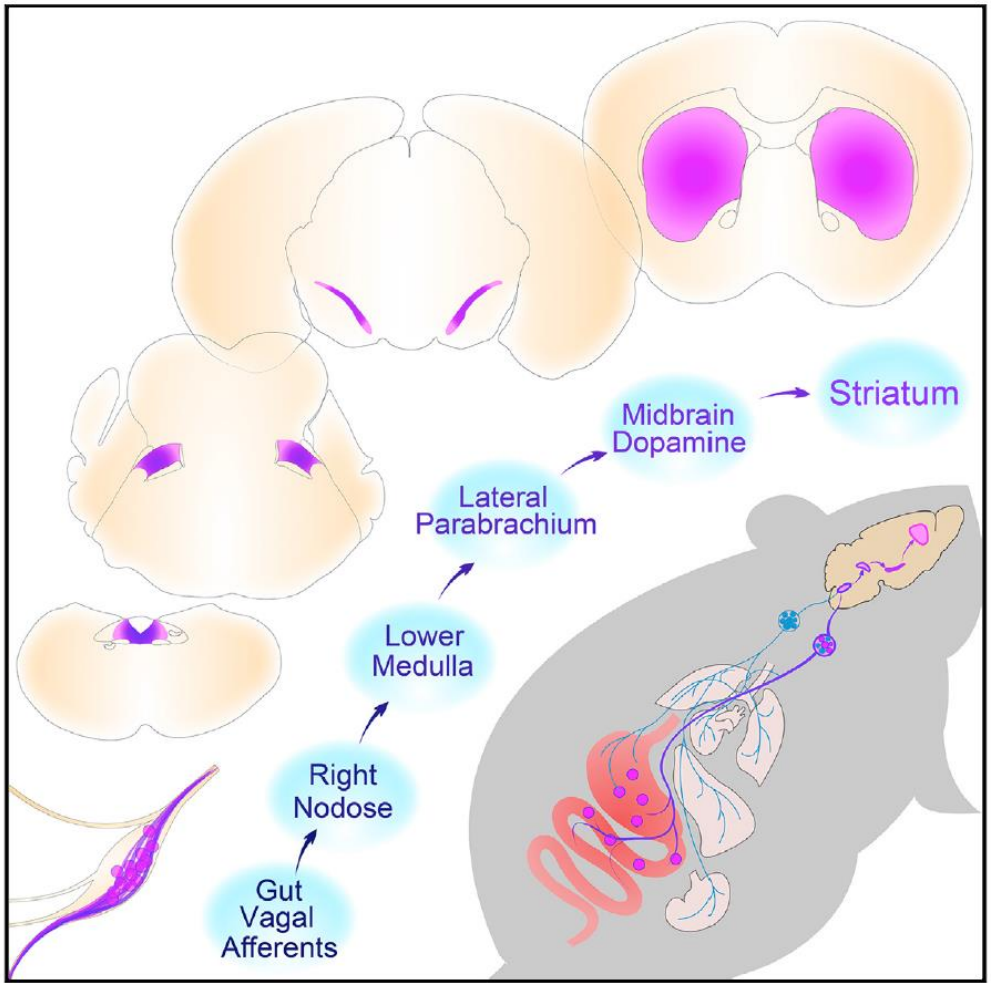
The neuropod cells. (Top left) Neuropod cells synapse with sensory neurons in the small intestine, as shown in a confocal microscopy image. Blue indicates all cells in villus; green indicates green fluorescent protein (GFP) in neuropod cell and sensory neurons. (Bottom left) This neural circuit is recapitulated in a coculture system between organoids and vagal neurons. Green indicates GFP in vagal neuron; red indicates tdTomato red fluorescence in neuropod cell. (Right) Neuropod cells transduce fast sensory signals from gut to brain. Scale bars, 10 μm.

Kaelberer *et al.*, *Science* **361**, 1219 (2018) 21 September 2018

Cell

A Neural Circuit for Gut-Induced Reward

Graphical Abstract



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In Brief

A gut-to-brain neural circuit establishes vagal neurons as an essential component of the reward neuronal pathway, linking sensory neurons in the upper gut to striatal dopamine release.

Highlights

最近のトピックス：キシロースイソメラーゼ

LETTER

https://doi.org/10.1038/s41586-018-0634-9

A gut microbial factor modulates locomotor behaviour in *Drosophila*

Catherine E. Schretter[1]*, Jost Vielmetter[2], Imre Bartos[3], Zsuzsa Marka[3], Szabolcs Marka[3], Su & Sarkis K. Mazmanian[1]*

While research into the biology of animal behaviour has primarily focused on the central nervous system, cues from peripheral tissues and the environment have been implicated in brain development and function[1]. There is emerging evidence that bidirectional communication between the gut and the brain affects behaviours including anxiety, cognition, nociception and social interaction[1–9]. Coordinated locomotor behaviour is critical for the survival and propagation of animals, and is regulated by internal and external sensory inputs[10,11]. However, little is known about how the gut microbiome influences host locomotion, or the molecular and cellular mechanisms involved. Here we report that germ-free status or antibiotic treatment results in hyperactive locomotor behaviour in the fruit fly *Drosophila melanogaster*. Increased walking speed and daily activity in the absence of a gut microbiome are rescued by mono-colonization with specific bacteria, including the fly

flies, whereas the number of (Fig. 1c–f). These data reveal speed and temporal patterns

The microbial community c species[15,16]. In laboratory-rais *L. brevis* and *Lactobacillus pla* munity affect distinct featur closely related microbial taxa c the host[15,17,18]. Accordingly, v mance was affected differentl similar levels of colonization (I with *L. brevis*—but not *L. plan* to correct changes in speed an and Extended Data Fig. 1b– host diet did not alter bacter

Nature 2018 doi: 10.1038/s41586-018-0634-9.

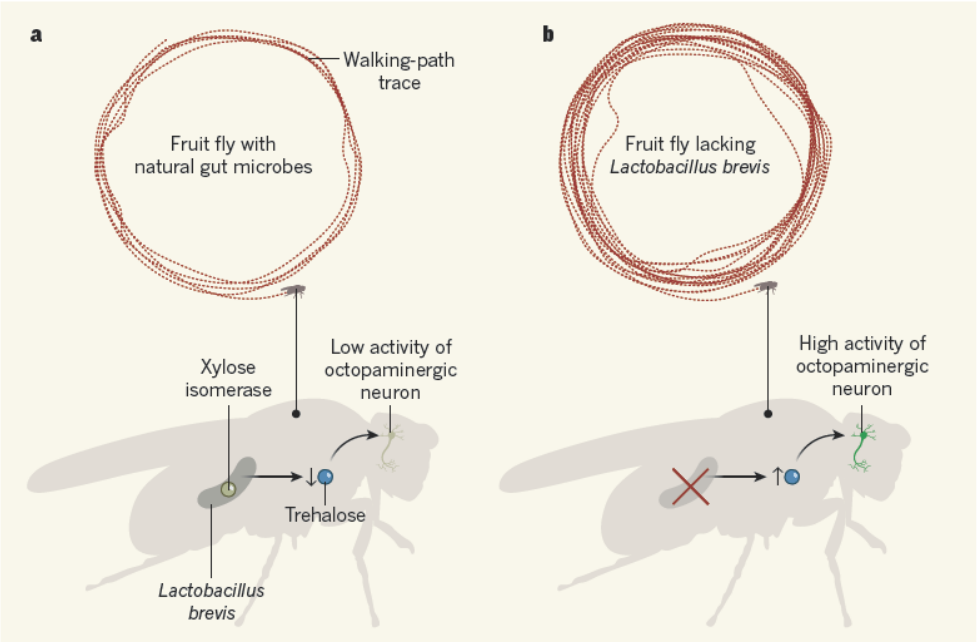


Figure 1 | A gut bacterium affects walking activity in the fruit fly *Drosophila melanogaster*. Schretter *et al.*[2] used imaging approaches to track fly movement and found that (**a**) fruit flies that have their natural gut microbes were less active than (**b**) flies that lack the gut bacterium *Lactobacillus brevis*. **a**, The authors reveal that the enzyme xylose isomerase produced by *L. brevis* is key to this phenomenon. This enzyme modifies certain sugars, which leads, by an unknown process, to a decrease in the level of the sugar trehalose in the body of flies in which this bacterial enzyme is present. The results of the authors' experiments are consistent with a model in which a decrease in trehalose is accompanied by a decrease in the activity of octopaminergic neurons (those that produce the neurotransmitter molecule octopamine) that regulate fly locomotion. **b**, Compared with flies that have their natural gut microbes, flies lacking *L. brevis* have higher levels of the sugar trehalose in their body and are proposed to have higher activity of octopaminergic neurons.

キシロースイソメラーゼ(Xylose isomerase):
D-キシロースをD-キシルロースに変換する酵素.
細菌や放線菌が産生.

Questions for future research

1.行動面への影響は?

2.メカニズムは?

3.ヒトでは?

The Treatment of Melancholia by the Lactic Acid Bacillus. (1) By J. GEORGE PORTER PHILLIPS, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P., Assistant Physician, Bethlem Royal Hospital.

MELANCHOLIA, with its attendant constipation and faulty alimentation, lends itself at once to a dietetic form of treatment.

Whether the constipation is dependent on defective innervation and is a direct symptom of melancholia or is the initial cause of this mental disturbance, it matters not so far as our endeavours in treatment are concerned.

It is obvious that the melancholiac, in the acute stages of his illness, struggles against great odds owing to the following facts: His alimentation is defective, his excretions are diminished, and, moreover, his whole system is in a state of auto-intoxication. In other words there is a general clogging of the metabolic processes. The disturbance of the alimentary tract tends to form a vicious cycle hindering the nervous system from obtaining an efficient and pure food supply.

We have ample evidence of this impaired metabolism with its toxæmia. The patient has a sallow, muddy complexion, a dry skin, a parched, furred tongue, a high-tension pulse, brittle nails and lustreless hair, a scanty high-coloured urine

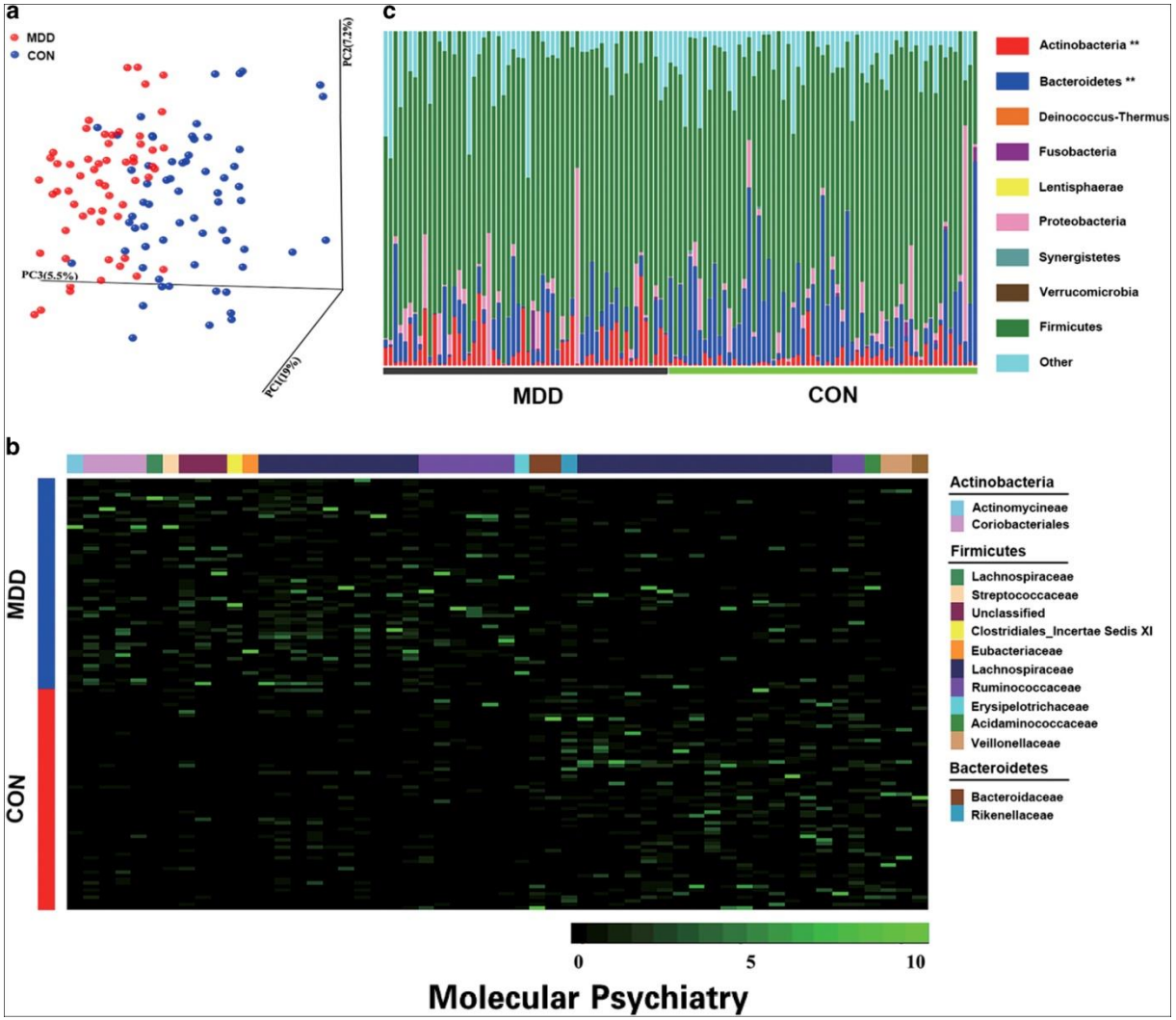
Melancholia患者18人に対し*Lactic acid bacillus*を投与し、臨床的効果を検討

結果：精神症状に関しては治癒11人，改善2人，不変4人，死亡1人であった。全例において便秘の改善と体重増加を認めた

(Phillips JGP　J Mental Sci 56:422-431, 1910)

うつ病と腸内細菌

Figure 2



The relative abundances of *Actinobacteria* and*Bacteroidetes* were significantly changed in MDD patients as compared with healthy controls. ***P*<0.01 by *t*-test.

Molecular Psychiatry (2016) 21, 786-796;
doi:10.1038/mp.2016.44

自閉スペクトラム症の腸内細菌叢

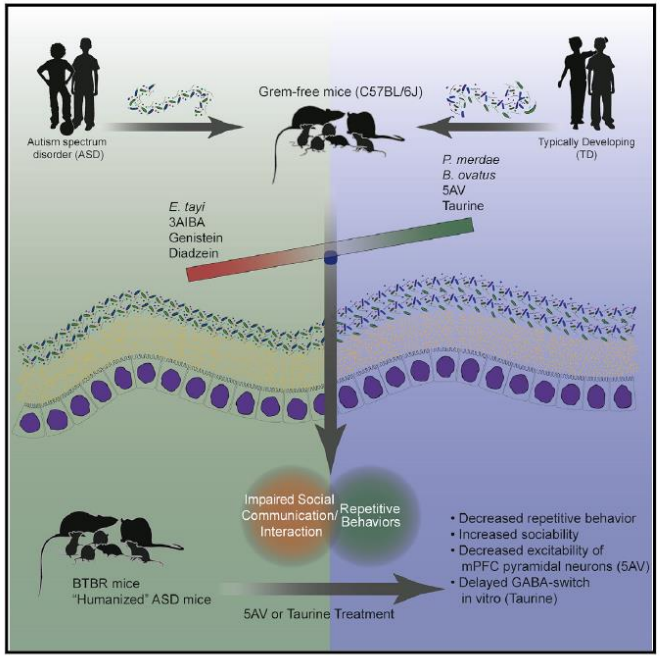
- 16S ribosomal RNAを指標
  - *Clostridium* ↑[1,2,3]
  - *Bacteroides* ↑[3,4]
  - *Bifidobacterium* ↓[3,4,5]
- *Clostridium*は消化器症状と関連[2]
- 総短鎖脂肪酸が少ない[5]

1. Finegold SM et al., *Clin Infect Dis*. 2002;35(Suppl 1):S6-S16
2. Parracho HM et al., *J Med Microbiol*. 2005;54(Pt 10):987-991
3. De Angelis M et al., *PLoS One*. 2013;8(10):e76993
4. Finegold SM et al., *Anaerobe*. 2010;16(4):444-453
5. Adams JB, et al., *BMC Gastroenterol*. 2011;11:22

Cell

Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice

Graphical Abstract



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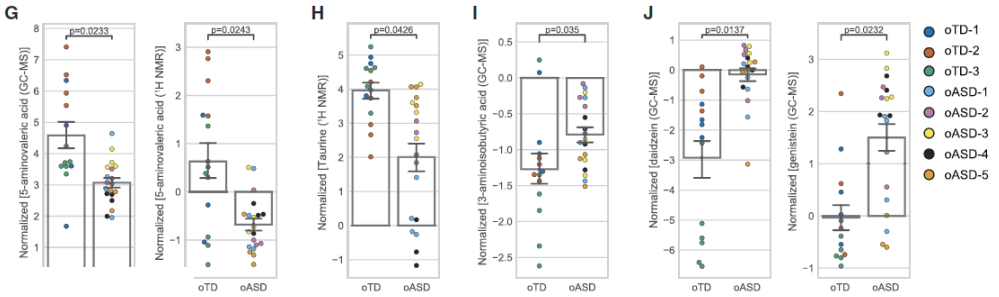
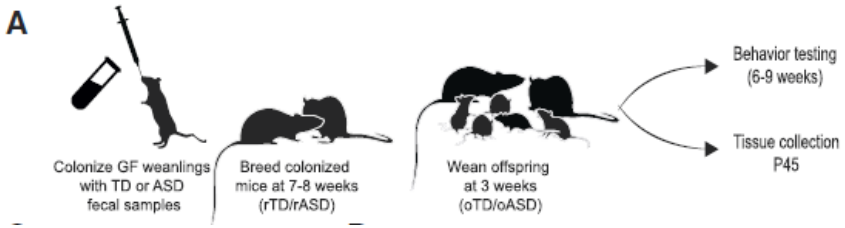
In Brief

Repetitive and social behavioral abnormalities in mice with microbiomes from patients with autism spectrum disorder can be corrected by the administration of specific metabolites.





神経性やせ症　診断基準
Anorexia nervosa　AN

- 極度の低体重
- 肥満に対する恐怖
- 体重・体型の感じ方の障害

DSM-5 精神疾患の診断・統計マニュアル,2014

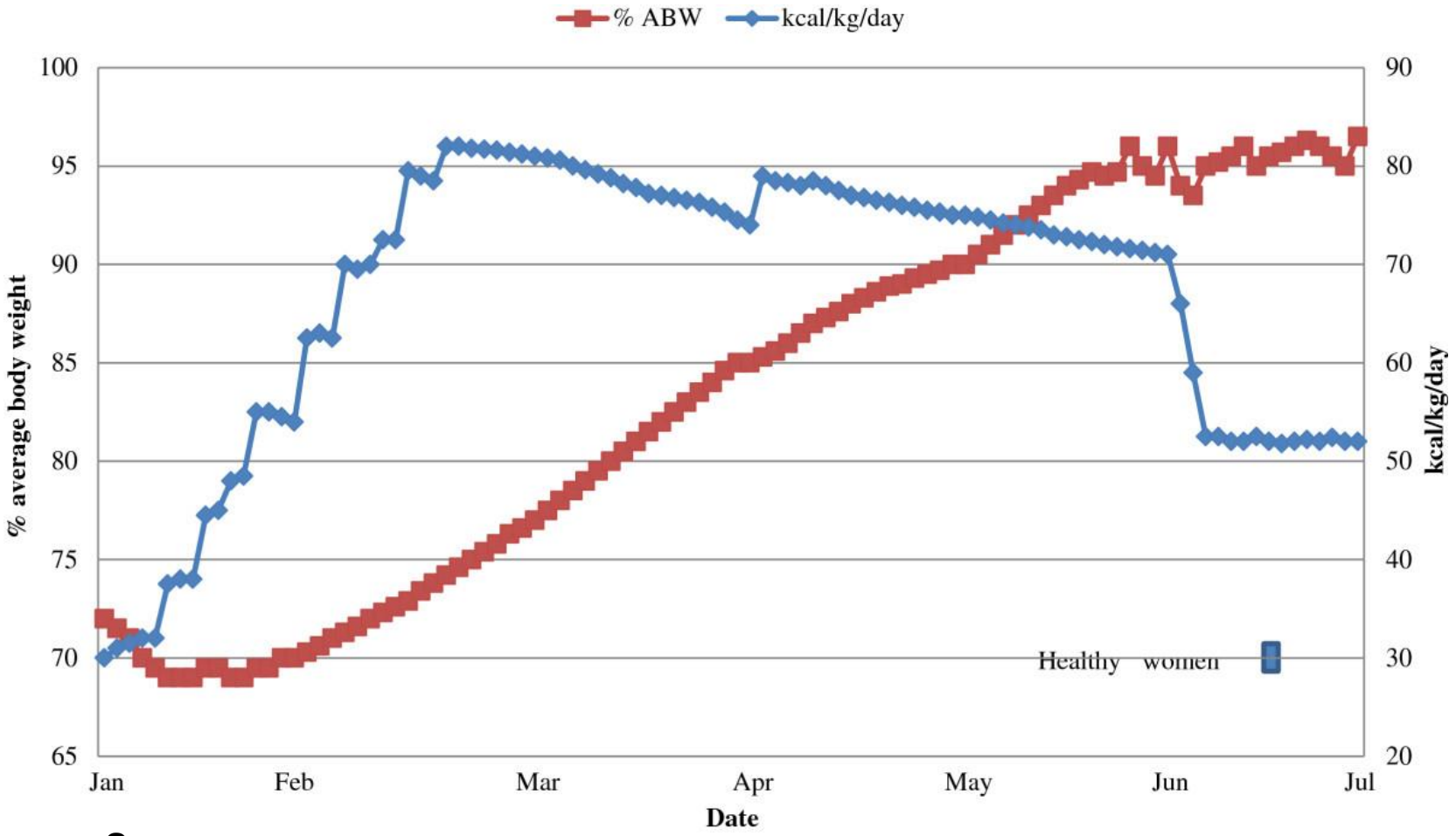
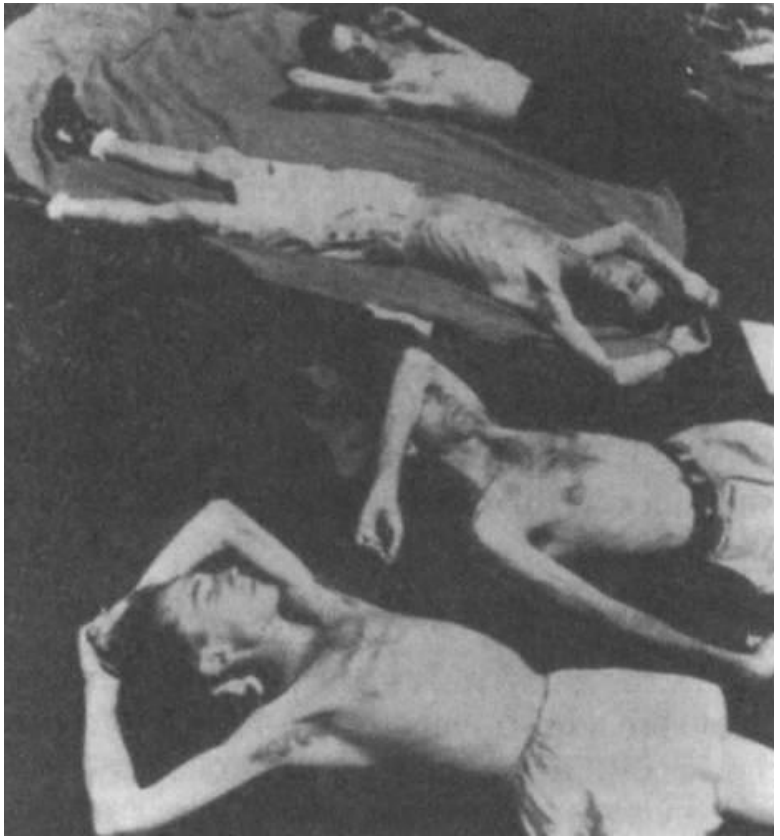


Figure 2.
Percent average body weight (% ABW) and kilocalories/kilogram per day (kcal/kg/day) in a typical course for a restricting-type anorexia nervosa individual who entered at 70% ABW. Individuals with anorexia nervosa tend to require escalating caloric intake in order to maintain a 1 to 1.5 kg/week weight gain during hospitalization (Kaye et al., unpublished data).
Marzola *et al. BMC Psychiatry* 2013 **13**:290 doi:10.1186/1471-244X-13-290

ミネソタ研究



被験者は“良心的徴兵拒否”をした健康男性36人。半年間、食事量を通常の半分に減らし（25%の体重減少）、身体面、精神面の変化を経時的に観察した。

ミネソタ研究：性格・行動の変化

- 無感動・抑鬱・疲労感が増した。
- イライラや気まぐれが多くなった。
- セルフコントロールの力・理解力・集中力が減退した。
- 外見や身だしなみについて無頓着になった。
- 騒音に敏感になるなど神経質になり、落ちつきのない、不安な状態になった。
- その日の食べ物の食べ方の配分について計画的になった。
- 食べ物の好き嫌いが無くなった。
- 自分の食べ物への所有欲が強くなった。
- 暖かい食べ物や飲み物を要求するようになった。
- 食べ物を多く見せかけたり、種類が多いように見せかけるようにした。

ANの持続・増悪因子としての腸内フローラ

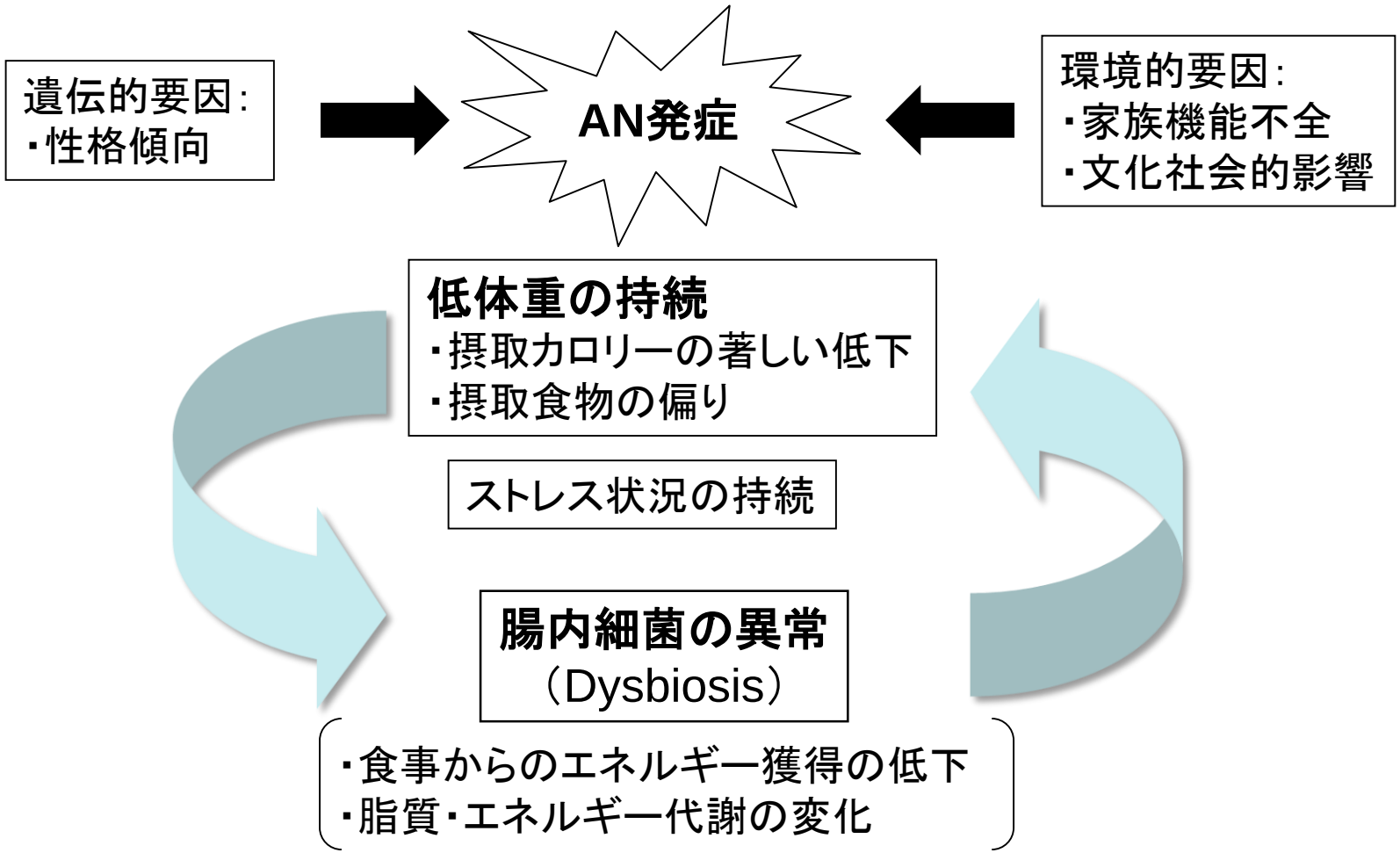


Table 3. Comparison of bacterial counts between the control subjects (CON) and anorexia nervosa (AN) patients.

	Log_{10} cells/g feces		p value	ES (r)
	CON (n = 21)	AN (n = 25)		
Total bacteria	11.1 ± 0.5	**10.5 ± 0.5***	**0.0002**	0.5560
C. coccoides group	10.0 ± 0.4	**9.3 ± 0.6***	**< .0001**	0.6015
C. leptum subgroup	10.4 ± 0.7	**9.6 ± 0.6***	**0.0006**	0.5138
B. fragilis group	10.5 ± 0.6	**9.6 ± 0.6***	**< .0001**	0.6376
Bifidobacterium	10.3 ± 0.7	9.9 ± 1.1	0.1729	0.2055
Atopobium cluster	9.3 ± 0.8	9.1 ± 1.2	0.7077	0.0553
Prevotella	6.9 ± 1.3	6.4 ± 0.8	0.3520	0.1645
Enterobacteriaceae	7.1 ± 0.9	7.0 ± 1.0	0.7046	0.0572
Enterococcus	6.2 ± 1.2	7.0 ± 1.2	0.0370	0.3144
Staphylococcus	5.3 ± 0.9	5.4 ± 0.8	0.9473	0.0098
Streptococcus	9.0 ± 0.7	**8.2 ± 0.8***	**0.0003**	0.5616
C. difficile	< 2.4	6.3 ± 1.1	NT	NT
C. perfringens	4.9 ± 1.3	4.6 ± 1.6	0.5478	0.1281
Total *Lactobacillus*	6.0 ± 1.1	5.7 ± 2.2	0.7065	0.0574
L. gasseri subgroup	5.4 ± 1.2	5.0 ± 1.8	0.2269	0.2136
L. reuteri subgroup	4.9 ± 1.0	5.0 ± 1.7	0.8748	0.0394
L. ruminis subgroup	4.2 ± 1.1	5.8 ± 2.1	0.1123	0.3969
L. plantarum subgroup	4.0 ± 0.8	3.5 ± 1.1	0.3421	0.2179
L. sakei subgroup	4.4 ± 1.3	3.9 ± 0.6	0.4743	0.1461
L. casei subgroup	5.8 ± 1.4	6.5 ± 1.4	0.3787	0.1921
L. brevis	5.3 ± 0.3	4.2 ± 0.4	0.2453	0.5810
L. fermentum	4.6 ± 0.7	8.7	0.2416	0.4781

*C, Clostridium; B, Bacteroides; L, Lactobacillus;*ES, effect size. NT means "not tested" because at least one group is below detection limits. The total count of *Lactobacillus* obtained by YIF-SCAN is expressed as the sum of the counts of 6 *Lactobacilli* subgroups and 2 species. An asterisk (*) indicates a significant difference between the AN and control group after the Bonferroni correction based on the number of tests (n = 21, p < 0.0024 (0.05/21)).

doi:10.1371/journal.pone.0145274.t003

Morita C, Tsuji H, Hata T, Gondo M, Takakura S, et al. (2015) Gut Dysbiosis in Patients with Anorexia Nervosa. PLoS ONE 10(12): e0145274. doi:10.1371/journal.pone.0145274
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0145274

Table 7. Comparison of organic acids and pH between the control subjects (CON) and anorexia nervosa (AN) patients.

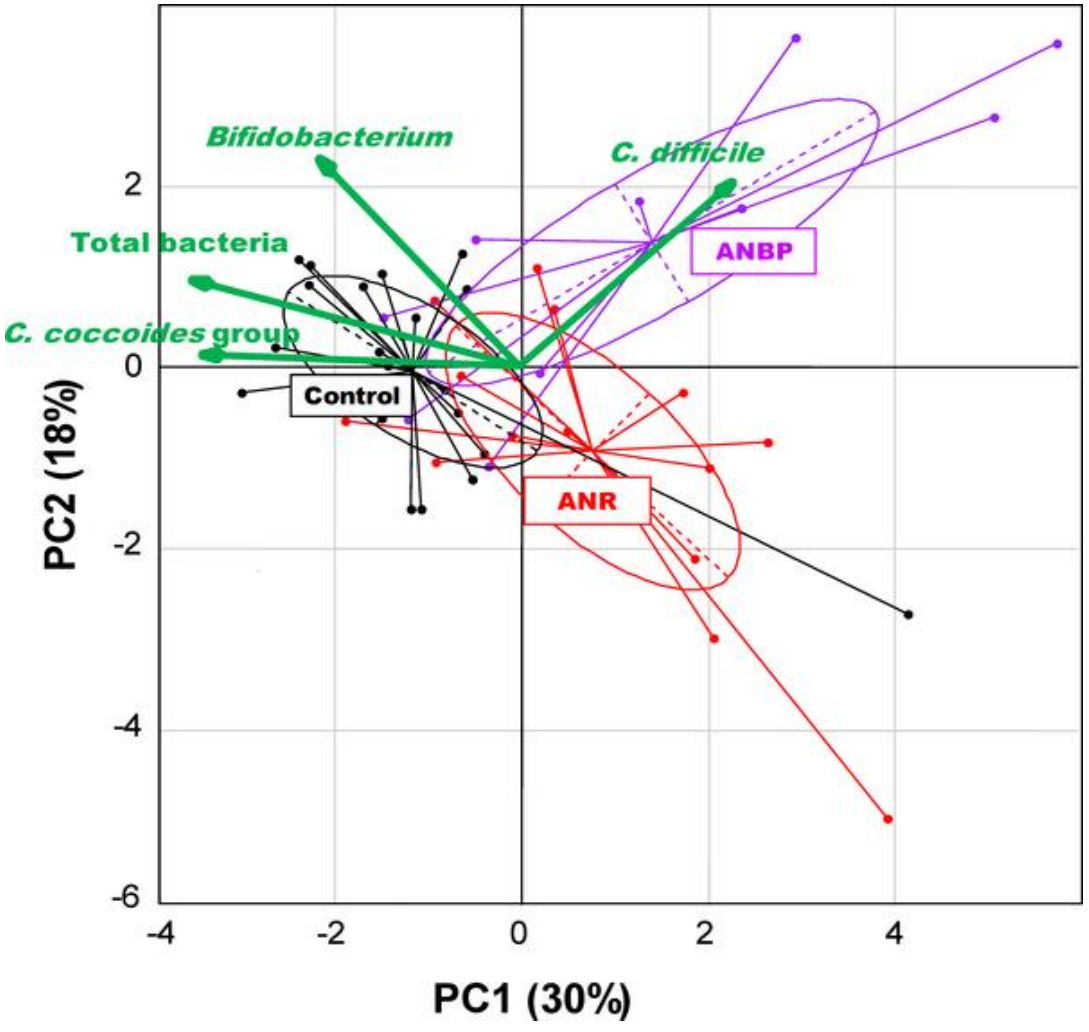
	μmol/g feces			
	Controls (n = 21)	**AN (n = 25)**	***p value***	**ES (*r*)**
Total organic acids	87.9 ± 43.9	54.3 ± 20.6	0.0049	0.4246
Succinic acid	5.9 ± 10.6	16.4 ± 18.0	0.3506	0.2200
Lactic acid	11.2 ± 12.8	0.9	0.2888	0.4743
Formic acid	0.1 ± 0.0	2.27 ± 2.71	0.0265	0.6405
Acetic acid	58.6 ± 27.0	**30.7 ± 13.2***	**0.0003**	0.5455
Propionic acid	15.2 ± 5.9	**9.3 ± 4.8***	**0.0010**	0.4957
Iso-butyric acid	1.2 ± 1.4	13.6 ± 8.2	0.0591	0.6674
Butyric acid	9.6 ± 7.5	3.8 ± 2.5	0.0082	0.5089
Isovaleric acid	3.1 ± 2.2	4.3 ± 1.4	0.18	0.3583
Valeric acid	4.2	4.7 ± 1.2	1	0
pH	6.74 ± 0.94	7.37 ± 0.86	0.0374	0.3103

ES: effect size. Total organic acid concentration is expressed as the sum of the concentrations of 9 acids. An asterisk (*) indicates a significant difference between the AN and control groups after a the Bonferroni correction based on the total number of tests (n = 11, $p < 0.0045$ (0.05/11)).

doi:10.1371/journal.pone.0145274.t007

Morita C, Tsuji H, Hata T, Gondo M, Takakura S, et al. (2015) Gut Dysbiosis in Patients with Anorexia Nervosa. PLoS ONE 10(12): e0145274. doi:10.1371/journal.pone.0145274
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0145274

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.

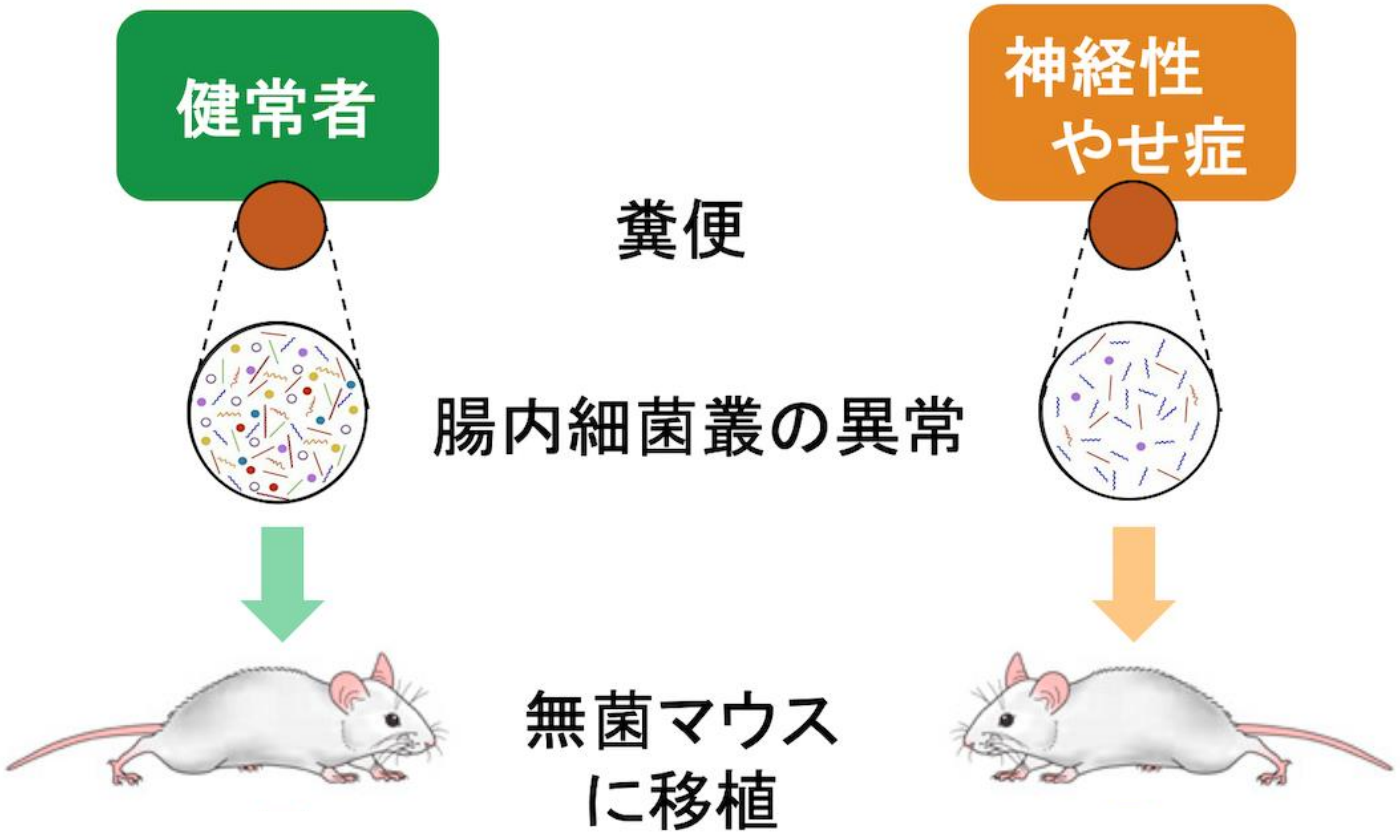


Morita C, Tsuji H, Hata T, Gondo M, Takakura S, et al. (2015) Gut Dysbiosis in Patients with Anorexia Nervosa. PLoS ONE 10(12): e0145274. doi:10.1371/journal.pone.0145274
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0145274

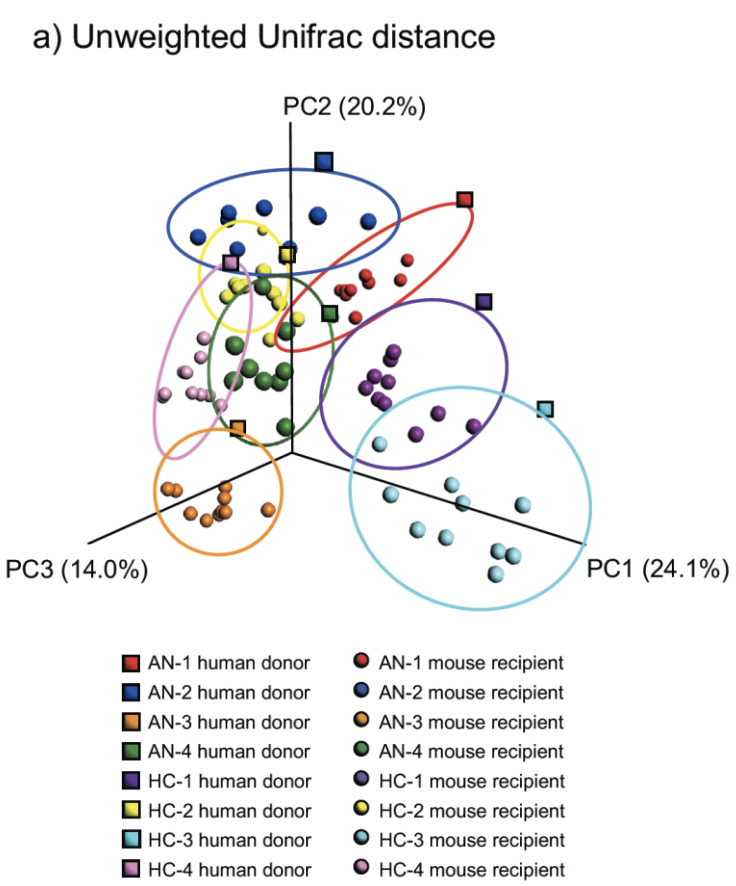
AN患者には腸内細菌叢の異常，

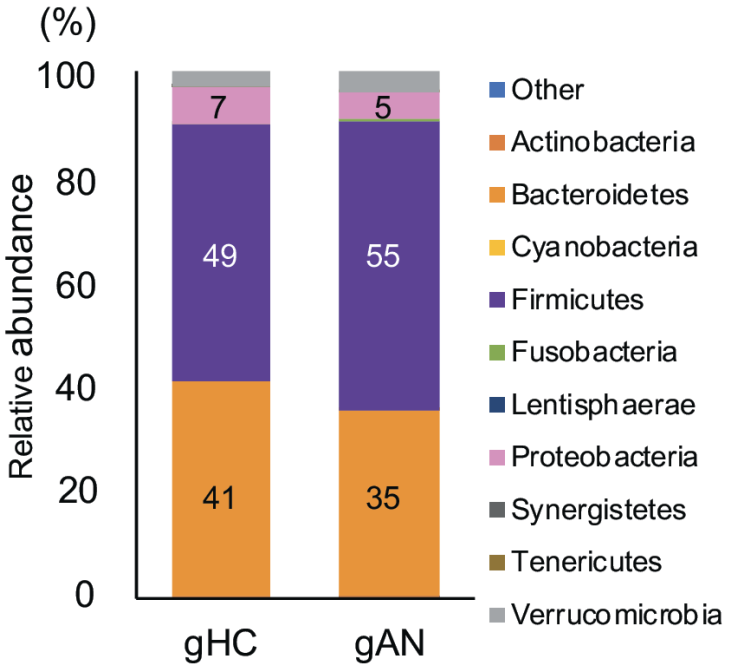
*“gut dysbiosis ”*が存在

- 体重増加不良との関連は？
- 行動や精神症状との関連は？


健常者
神経性
やせ症
糞便
腸内細菌叢の異常
無菌マウス
に移植

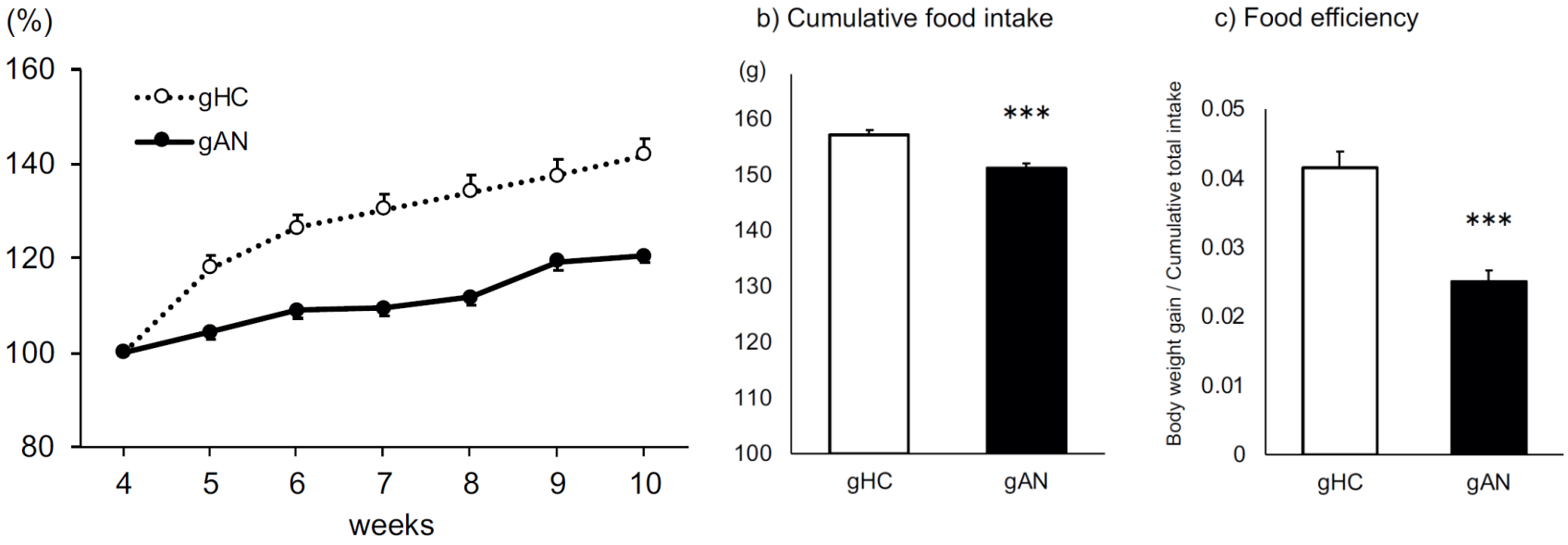
ドナー（ヒト）とレシピエント（マウス）の腸内菌叢





(Hata et al. Endocrinology, in press)

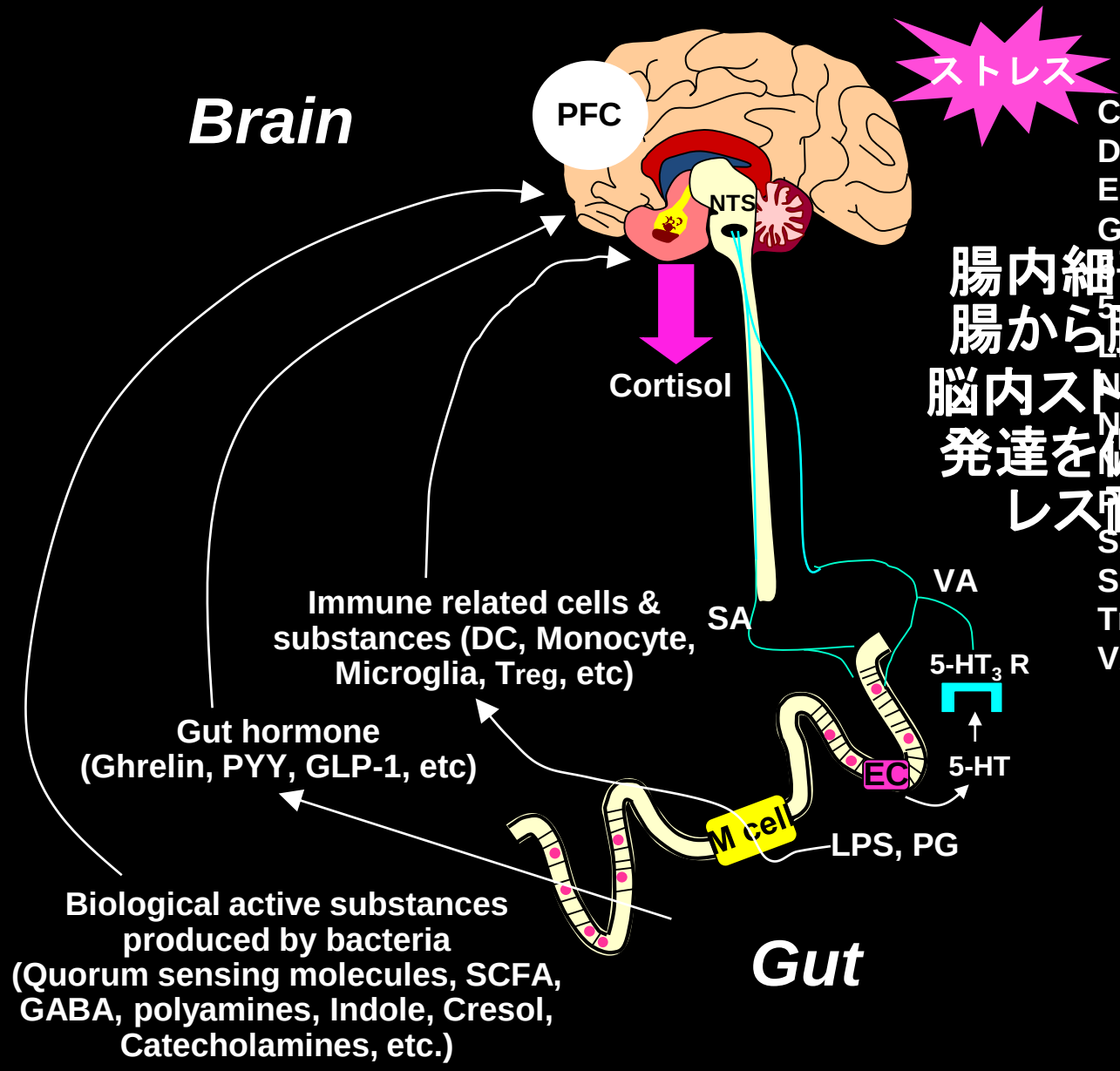
体重, 食事摂取量, および栄養効率



AN型マウスは健常型マウスと比較し、体重増加が不良であり、
栄養効率も低い

(Hata et al. Endocrinology, in press)

腸内フローラと脳腸相関：ストレス応答への影響



CA: catecholamines
DC: dendritic cell
EC: enterochromaffin cell
GABA: γ-aminobutyric acid
5-HT: 5-hydroxytryptamine
5-HT3 R: 5-HT type 3 receptor
LPS: lipopolysaccharide
NTS: nucleus tractus solitarius
NG: nodose ganglia
NO: nitric oxide
PG: peptidoglycan
SA: spinal afferent nerve
SCFA: short-chain fatty acid
Treg: regulatory T cell
VA: vagal afferent nerve

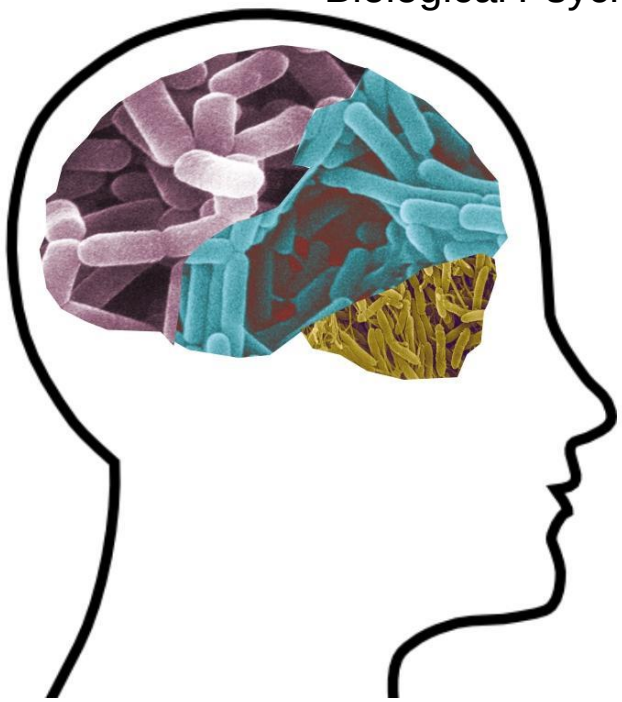
腸内細菌に端を発した腸から脳への信号は脳内ストレス制御機構の発達を促し、宿主のストレス耐性を高める

Psychobiotics: A Novel Class of Psychotropic

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

Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. So far, psychobiotics have been most extensively studied in a liaison psychiatric setting in patients with irritable bowel syndrome, where positive benefits have been reported for a number of organisms including *Bifidobacterium infantis*. Evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Such benefits may be related to the anti-inflammatory actions of certain psychobiotics and a capacity to reduce hypothalamic-pituitary-adrenal axis activity. Results from large scale placebo-controlled studies are awaited.

Biological Psychiatry 74:720–726, 2013



From *Probiotics* to *Psychobiotics*!

謝　辞

九州大学大学院　心身医学
九州大学病院　心療内科

ご清聴ありがとうございました

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