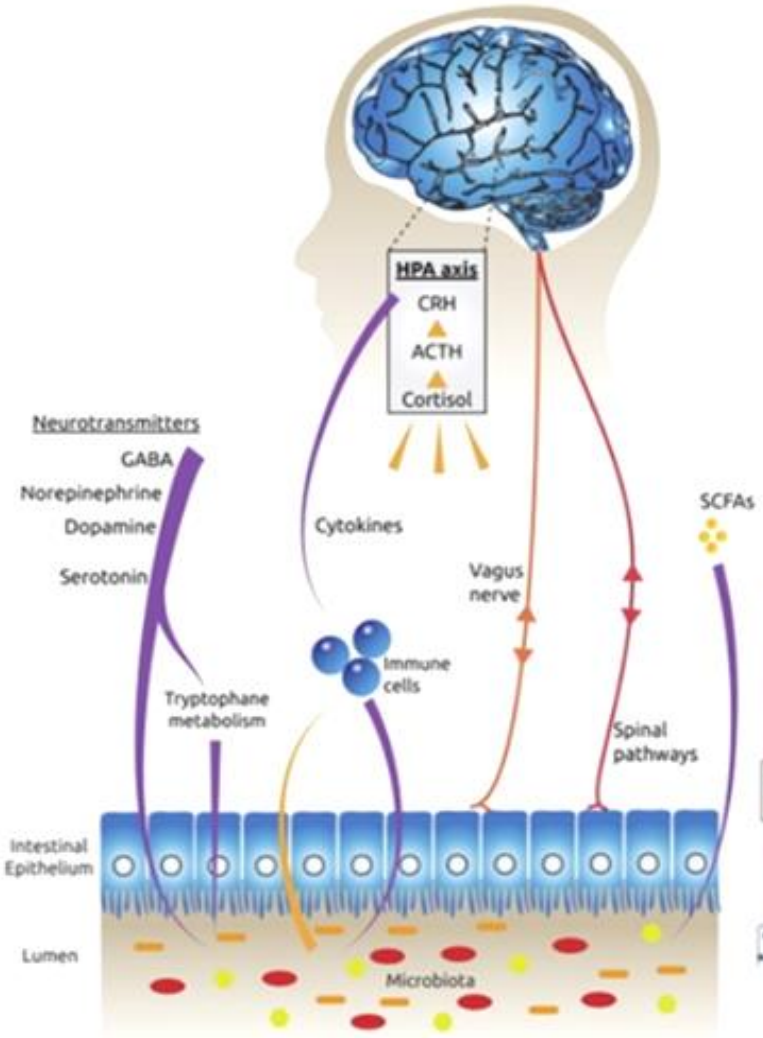
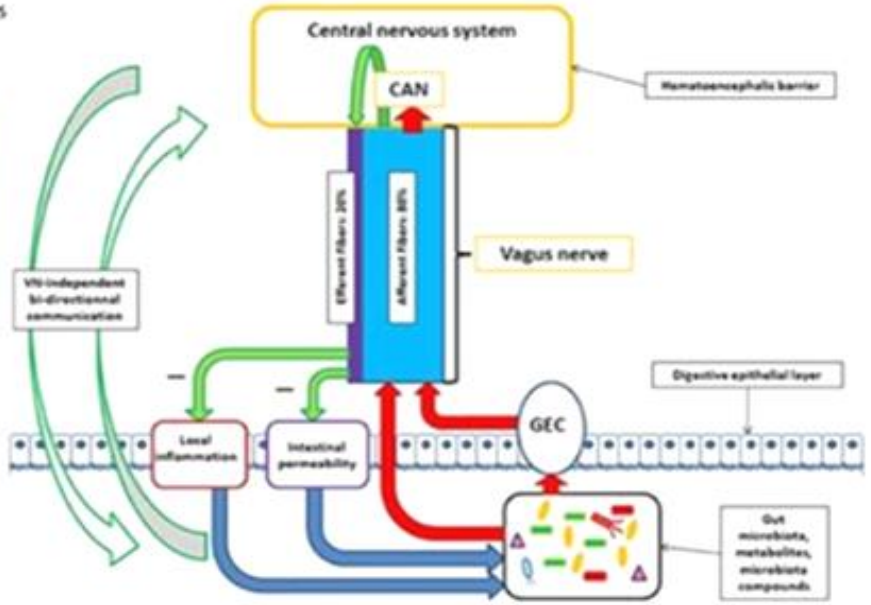
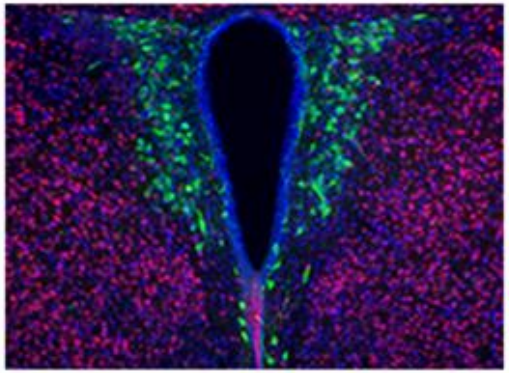
Neurosciences 2018

The latest news to improve our health

Hala El-Makhour

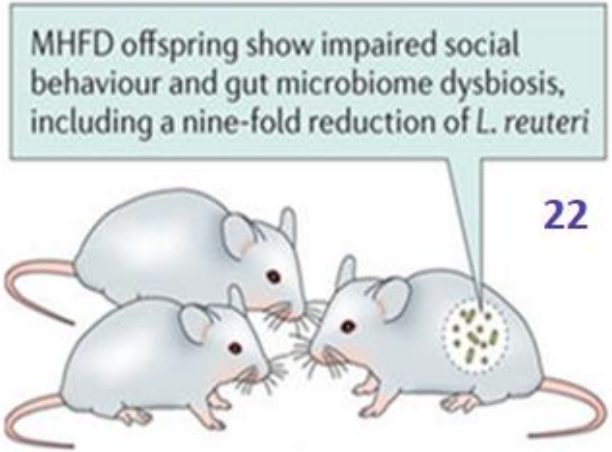






Oxytocin Levels are reduced in the Hypothalamus of MHFD Offspring.

P. 27



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PRINCETON UNIVERSITY

Office of Communications

Feb. 6, 2018

Joshua Rabinowitz

"Mouse study reveals gut effects of too much fructose"

https://www.princeton.edu/news/2018/02/06/mouse-study-reveals-gut-effects-too-much-fructose

In the study, Rabinowitz and his colleagues studied the path of isotope-labeled fructose through the digestive systems of laboratory mice.
90 percent of the fructose is cleared by the small intestine in mice. "We can offer some reassurance — at least from these animal studies — that fructose from moderate amounts of fruits will not reach the liver," he said. However, the small intestine probably starts to get overwhelmed with sugar halfway through a **can of soda or large glass of orange juice.**

The researchers observed that excess fructose that is not absorbed by the small intestine continues through the intestine into the colon. As a consequence, it also comes into contact with the natural microbiotic flora of the large intestine and colon, known as the microbiome.

"The microbiome is designed to never see sugar," Rabinowitz said. "One can eat an infinite amount of carbohydrates, and there will be nary a molecule of glucose that enters the microbiome. But as soon as you drink the soda or juice, the microbiome is seeing an extremely powerful nutrient that it was designed to never see."

While the study did not show that fructose influences the microbiome, the authors suggest an effect is likely and should be studied further to learn more about the biological consequences of high sugar intake.

The investigators also found that the small intestine clears fructose more efficiently after a meal. "We saw that feeding of the mice prior to the sugar exposure enhanced the small intestine's ability to process fructose," said Rabinowitz. "And that protected the liver and the microbiome from sugar exposure."

The researchers theorize that in a fasting state, such as upon awakening or in the mid-afternoon, one is extra vulnerable to fructose due to a lessened ability to process it in the small intestine.

Although the study was conducted in mice, Rabinowitz encourages "the most old-fashioned advice in the world" for humans: limit sweets to moderate quantities after meals, and do not have sweet drinks away from mealtime.

https://www.princeton.edu/news/2018/02/06/mouse-study-reveals-gut-effects-too-much-fructose

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0190368

Published: January 2, 2018

The type of fat in the diet determinates the characteristics of gut microbiota, exerting a major role in the development of metabolic syndrome. We hypothesize that a diet enriched with extra virgin olive oil (EVOO) has a distinctive effect on the intestinal microbiome in comparison with an enriched butter diet (BT).

Swiss Webster mice were fed standard (SD) or two high fat diets enriched with EVOO or butter. Hormonal, physiological and metabolic parameters were evaluated. At the end of the feeding period, DNA was extracted from faeces and the 16S rRNA genes were pyrosequenced. Among the main significant differences found, BT triggered the highest values of systolic blood pressure, correlating positively with the percentage of *Desulfovibrio* sequences in faeces, which in turn showed significantly higher values in BT than in EVOO. EVOO had the lowest values of plasmatic insulin, correlating inversely with *Desulfovibrio*, and had the lowest plasmatic values of leptin which correlated inversely with *Sutterellaceae*, *Marispirillum* and *Mucilaginibacter dageonensis*, the three showing significantly higher percentages in EVOO. The lowest total cholesterol levels in plasma were detected in SD, correlating positively with *Prevotella* and *Fusicatenibacter*, both taxa with significantly greater presence in SD. These results may be indicative of a link between specific diets, certain physiological parameters and the prevalence of some taxa, supporting the possibility that in some of the proposed effects of virgin olive oil the modulation of intestinal microbiota could be involved.

Fermented milk product containing the heat-killed probiotic strain *Lactobacillus paracasei* CBAL74 induces changes in the gut microbiota, promoting the development of butyrate producers.

https://www.ncbi.nlm.nih.gov/pubmed/28733284

We recently demonstrated that cow's milk fermented with the probiotic *Lactobacillus paracasei* CBA L74 (FM-CBAL74) reduces the incidence of respiratory and gastrointestinal tract infections in young children attending school. We investigated whether FM-CBAL74 could regulate gut microbiota composition and butyrate production. We randomly selected 20 healthy children (12 to 48 months) from the previous randomized controlled trial, before (t0) and after 3 months (t3) of dietary treatment with FM-CBAL74 (FM) or placebo (PL).

Fecal microbiota was profiled using 16S rRNA gene amplicon sequencing, and the fecal butyrate concentration was also measured. Microbial alpha and beta diversities were not significantly different between groups prior to treatment.

FM-CBAL74 but not PL treatment increased the relative abundance of Lactobacillus Individual Blautia, Roseburia, and Faecalibacterium oligotypes were associated with FM-CBAL74 treatment and demonstrated correlative associations with immune biomarkers.

Accordingly, PICRUSt analysis predicted an increase in the proportion of genes involved in butyrate production pathways, consistent with an increase in fecal butyrate observed only in the FM group.

Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort

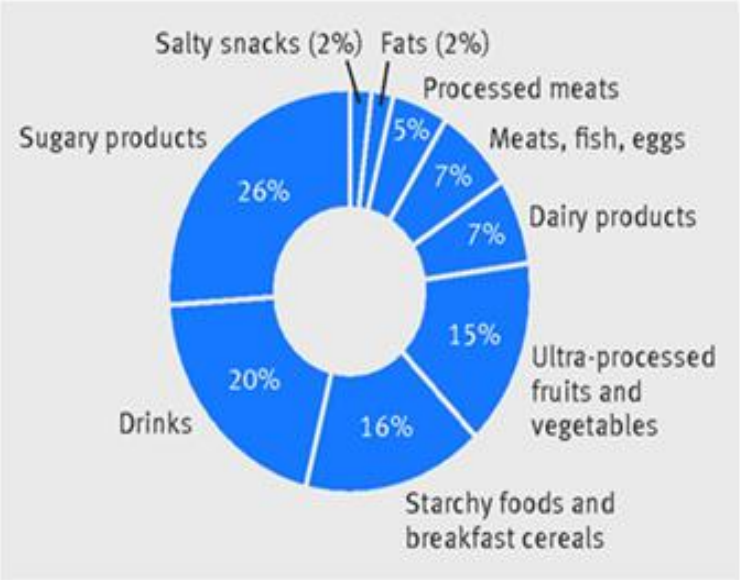
Published 14 February 2018

BMJ 2018; 360:k322

https://www.bmj.com/content/360/bmj.k322

Setting and participants 104 980 participants aged at least 18 years (median age 42.8 years) from the French NutriNet-Santé cohort (2009-17)

Conclusions In this large prospective study, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer.



Main food groups contributing to ultra-processed food intake were **sugary products** (26%) and drinks (20%), followed by **starchy foods and breakfast cereals** (16%) and ultra-processed fruits and vegetables (15%)

Animal studies have shown that some additives are "quite good candidates" for being carcinogenic, Touvier said. Ultra-processed foods occupy a growing part of the world's diet.

A 2016 study found that 60% of the calories in the average American diet come from this kind of food. A 2017 study found that they make up **50% of the Canadian diet.**

TOP 10
WORST PROCESSED FOODS

1 Chicken nuggets 24%
2 Hot dogs 19%
3 Fake cheese 14%
4 Lunchables 13%
5 Spam 9%
6 Twinkies 5%
7 Soda 5%
8 Artificial sweeteners 4%
9 Diet versions 4%
10 French fries 3%

Health Beat:

Caloric restriction is a win-win

Melanie Falcon

Jean-Pierre Issa

Feb 23, 2018

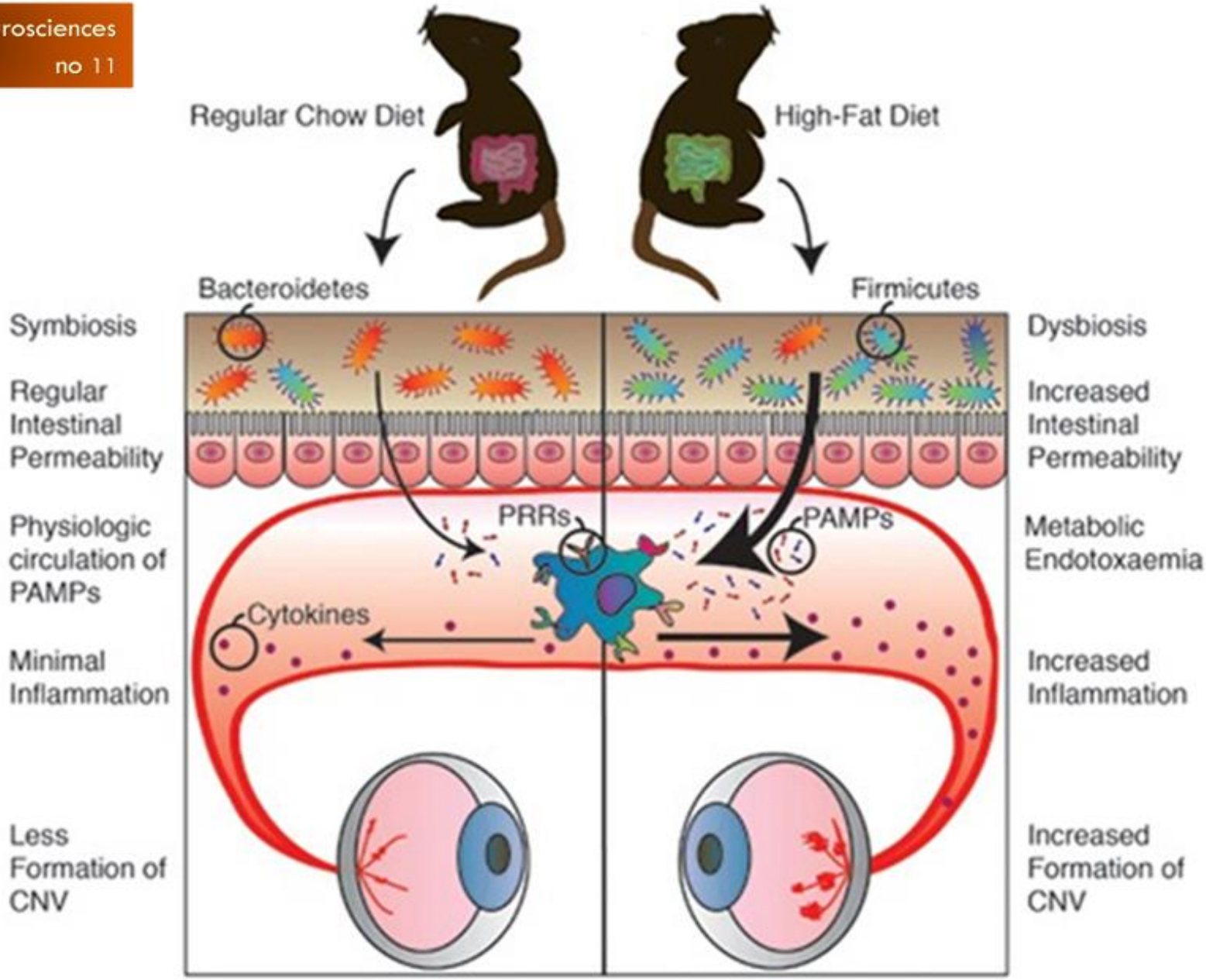
PHILADELPHIA - Dr. Jean-Pierre Issa conducts research into caloric restriction and its impact on mice. He is focused on the long-term effects on stem cells.

"So if our stem cells remain healthier, then they are more available to repair tissues, to fix injuries, to fix heart attacks, and to live longer," explained Issa.

Calorically restricted mice, at least some of them, not only live longer but show fewer signs of aging.

"In mice, you can look at their fur, look at their hair. As in humans, it changes color with age, but in mice that are calorie-restricted, it retains a youthful appearance," Issa said. "The calorie restriction seemed to somehow promote the health of cells and keep their cellular identity intact."

https://www.templehealth.org/News/TempleScientistsUncoverMechanismBehindbrCalorieRestrictionandLengthenedLifespan?showBack=true&PageIndex=0



https://nouvelles.umontreal.ca/en/article/2016/11/15/microbes-in-your-gut-influence-major-eye-disease/

https://onlinelibrary.wiley.com/doi/full/10.15252/emmm.201606531

Przemyslaw Sapieha

We show that high-fat diets induce gut

microbial dysbiosis, resulting in heightened intestinal permeability,

which leads to chronic low-grade

inflammation and ultimately increased choroidal neovascularization (CNV)

- A high-fat diet (HFD) induces a shift in commensal gut microbiota and increases permeability of the gut barrier.
- Intestinal dysbiosis increases circulating pathogen-associated molecular patterns (PAMPs), leading to low-grade endotoxemia that triggers an inflammatory response through pattern recognition receptors (PRRs).
- Increased concentrations of circulating and local inflammatory cytokines such as IL-6, IL-1β, TNF-α, and VEGF-A exacerbate CNV.
- Microbiotal transplants confirm that HFD aggravates CNV through gut microbiota.

https://onlinelibrary.wiley.com/doi/full/10.15252/emmm.201606531

C57BL/6J mice were raised under sterile barrier conditions and placed on a regular-chow diet (RD; 16% kcal fat) or high-fat diet (HFD; 60% kcal fat), from 6 weeks of age (Fig 1A). As expected, upon killing at 13 weeks, HFD-fed mice gained over 50% more weight than control RD-fed mice (Fig 1B and C). At 11 weeks of life, we subjected mice to a laser-induced photocoagulation model of CNV, where perforation of Bruch's membrane initiates sprouting of subretinal blood vessels from the choroid, thus mimicking NV AMD (Lambert *et al*, 2013). Quantification of FITC–dextran-perfused neovessels over isolectin B4 (IB4)-labeled impact area by confocal imaging 14 days after laser burn revealed a robust 60% increase in CNV in HFD-fed mice when compared to RD controls (Fig 1D and E). https://onlinelibrary.wiley.com/doi/full/10.15252/emmm.201606531

High-fat diet modulates gut microbiota and exacerbates CNV

EMBO Mol Med. 2016 Dec; 8(12): 1366–1379.

Published online 2016 Nov 15. doi: 10.15252/emmm.201606531

PMCID: PMC5167134

PMID: 27861126

C57BL/6J

C57BL/6, It is the most widely used "genetic background" for genetically modified mice for use as models of human disease. Wikipedia

BRAIN
RESEARCH
INSTITUTE
UCLA

UCLA Newsroom

Fernando Gomez-Pinilla

Fructose Alters Brain Genes, Can Lead to Disease

A range of diseases — from diabetes to cardiovascular disease, and from Alzheimer's disease to attention deficit hyperactivity disorder — are linked to changes to genes in the brain.

A study by scientists from UCLA life sciences and the school of medicine has found that hundreds of those genes can be damaged by fructose, a sugar that's common in the Western diet, in a way that could lead to those diseases.

However, the researchers also discovered good news: An omega-3 fatty acid known as docosahexaenoic acid, or DHA, seems to reverse the harmful changes produced by fructose.

http://newsroom.ucla.edu/releases/fructose-alters-hundreds-of-brain-genes-which-can-lead-to-a-wide-range-of-diseases

Nutrition plays a significant role in the increasing prevalence of metabolic and brain disorders.

Here we employ systems nutrigenomics to scrutinize the genomic bases of nutrient–host interaction underlying disease predisposition or therapeutic potential. We conducted transcriptome and epigenome sequencing of hypothalamus (metabolic control) and hippocampus (cognitive processing) from a rodent model of fructose consumption.

Tests on the rats revealed more major differences:

The rats receiving a high-fructose diet had much higher blood glucose, triglycerides and insulin levels than the other two groups.

Those results are significant because in humans, elevated glucose, triglycerides and insulin are linked to obesity, diabetes and many other diseases.

Reference: "Systems Nutrigenomics Reveals Brain Gene Networks Linking Metabolic and Brain Disorders," *EBioMedicine*, April 13, 2016

The researchers trained rats to escape from a maze, and then randomly divided the animals into three groups.

For the next six weeks, one group of rats drank water with an amount of fructose that would be roughly equivalent to a person drinking a liter of soda per day.

The second group was given fructose water and a diet rich in DHA.

The third received water without fructose and no DHA.

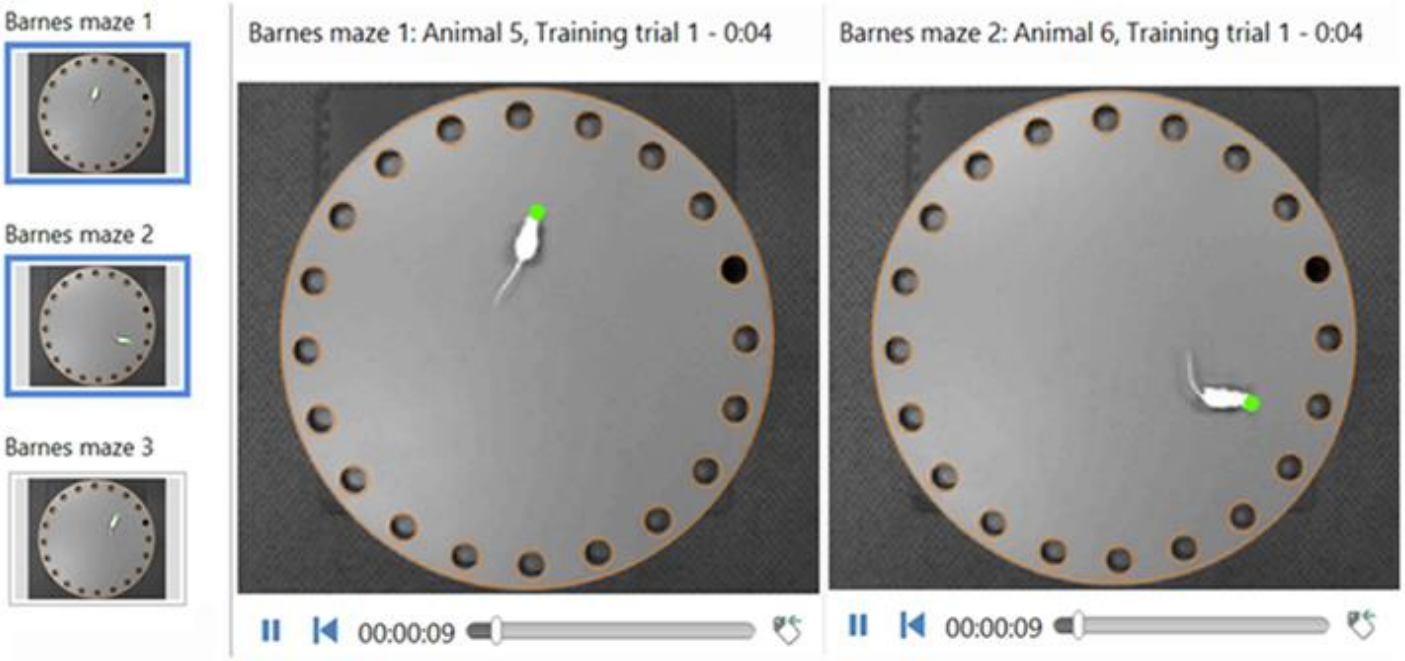
After the six weeks, the rats were put through the maze again.

The animals that had been given only the fructose navigated the maze about half as fast than the others. The rats that had been given fructose and DHA, however, showed very similar results to those that only drank water — which strongly suggests that the DHA eliminated fructose's harmful effects.

Rats were trained in the Barnes maze test for 5 days to learn the task

The basic function of Barnes maze is to measure the ability of a mouse to learn and remember the location of a target zone. The Barnes maze is a relatively simple design of a circular platform top with several holes equally spaced around the perimeter edge. All but one of the holes are false-bottomed or blind-ending, while one leads to an escape cage. Mildly aversive stimuli (e.g. bright overhead lights) provide motivation to locate the escape cage. Latency to locate the escape cage can be measured during the session.

Source: "Barnes Maze Testing Strategies with Small and Large Rodent Models" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140524/



SAS Sprague Dawley Rat

Male Sprague – Dawley rats (Charles River Laboratories, Inc., MA, USA) of 2 months old weighing 200-220 g were randomly assigned to 15% fructose treatment (n = 8, 15% w/v fructose in the drinking water), 15% fructose plus an omega-3 fatty acid diet rich in DHA (n = 8; 0.5% of flaxseed oil supplying ALA and 1.2% of DHA capsule oil, Nordic Naturals, Inc., CA, USA), or a control group (n = 8, without fructose in drinking water or DHA supplement) for six weeks.

The fructose intake level is approximately equivalent to long-term daily consumption of 130 g sugar in 1–2 l soda drinks in a 60 kg human.

The total fat content in the control and DHA diets was 10 g per 100 g of diet.

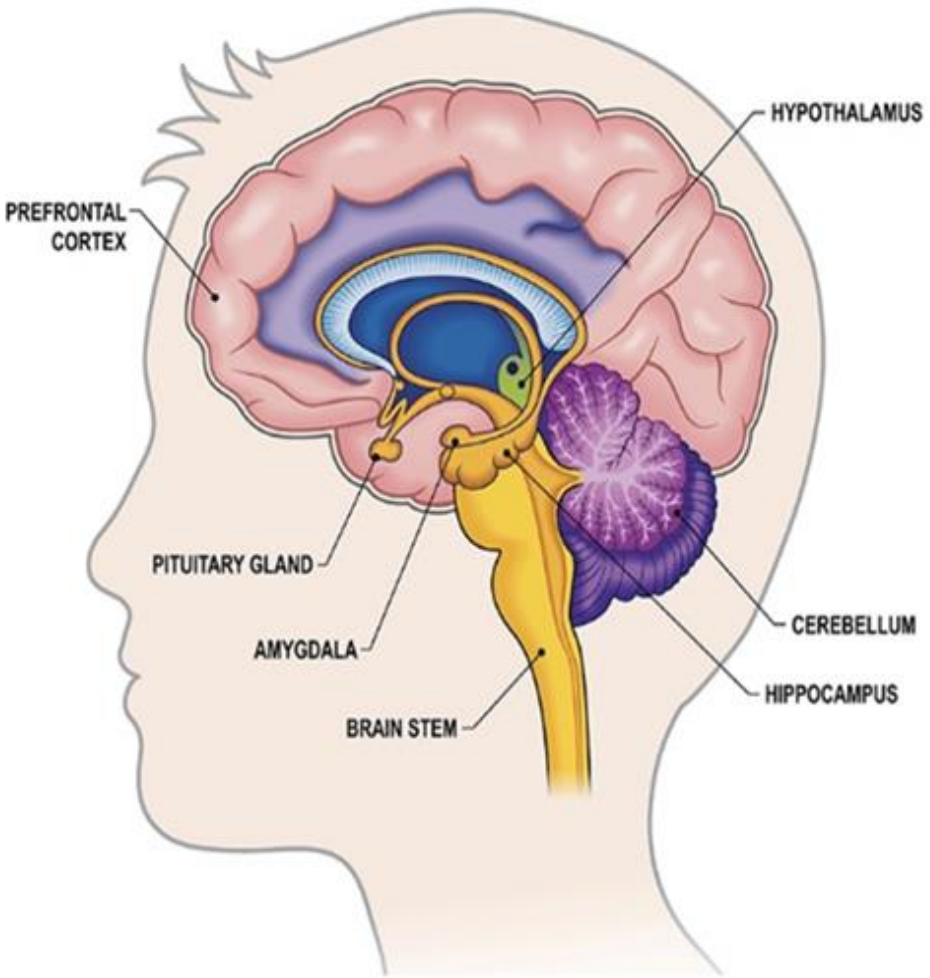
Source:

The rats were then examined for changes in MetD-related phenotypes (serum levels of insulin, glucose, and triglycerides, and insulin resistance index (fasting glucose [mg/dl] × fasting insulin [ng/ml] / 16.31)).

http://newsroom.ucla.edu/releases/fructose-alters-hundreds-of-brain-genes-which-can-lead-to-a-wide-range-of-diseases Fructose alters hundreds of brain genes, which can lead to a wide range of diseases"Systems Nutrigenomics Reveals Brain Gene Networks Linking Metabolic and Brain Disorders," *EBioMedicine*, April 13, 2016

We focus our study on two key regions in the rodent brain that are important for the regulation of metabolism (hypothalamus) and cognition (hippocampus), and therefore can play a major role in fructose-induced metabolic and brain dysregulation as well as DHA-mediated recovery.

Mice were sacrificed, and hypothalamus and hippocampus were dissected out, flash frozen, and stored at − 70 °C for transcriptome and DNA methylome sequencing experiments.



The research team sequenced more than 20,000 genes in the rats' brains, and identified more than 700 genes in the hypothalamus (the brain's major metabolic control center) and more than 200 genes in the hippocampus (which helps regulate learning and memory) that were altered by the fructose. The altered genes they identified, the vast majority of which are comparable to genes in humans, are among those that interact to regulate metabolism, cell communication and inflammation. Among the conditions that can be caused by alterations to those genes are Parkinson's disease, depression, bipolar disorder, and other brain diseases, said Yang.

Of the 900 genes they identified, the researchers found that two in particular, called Bgn and Fmod, appear to be among the first genes in the brain that are affected by fructose.

Once those genes are altered, they can set off a cascade effect that eventually alters hundreds of others.

The research also uncovered new details about the mechanism fructose uses to disrupt genes. The scientists found that fructose removes or adds a biochemical group to cytosine, one of the four nucleotides that make up DNA.

This type of modification plays a critical role in turning genes "on" or "off."

References: "Systems Nutrigenomics Reveals Brain Gene Networks Linking Metabolic and Brain Disorders," *EBioMedicine*, April 13, 2016

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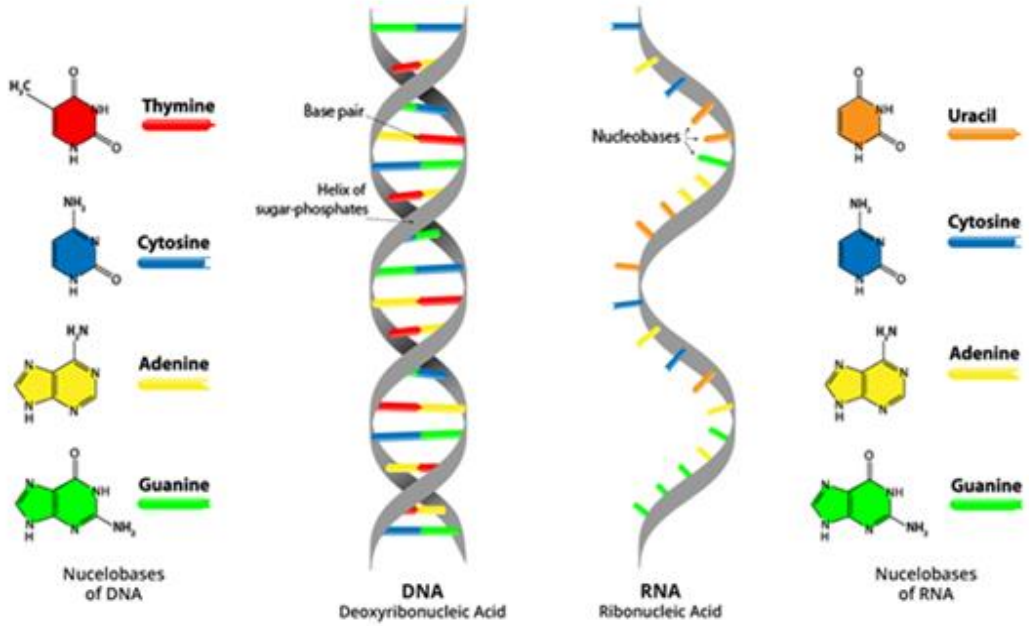
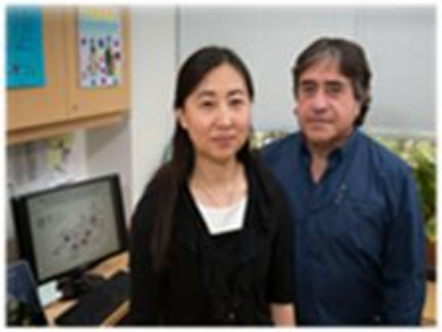




DHA changes not just

one or two genes,

it seems to push the entire gene pattern back to normal,

which is remarkable

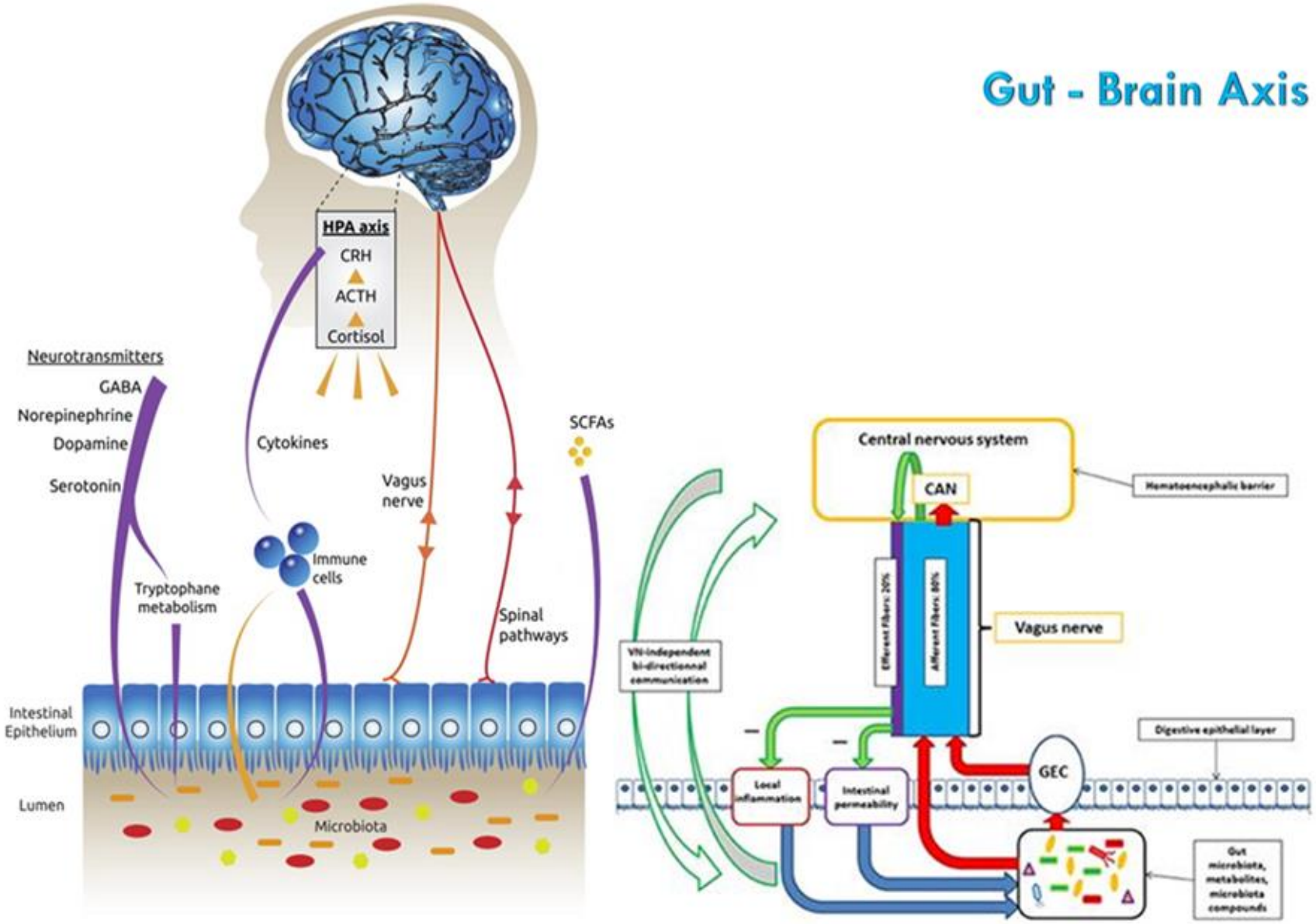
DHA occurs naturally in the membranes of our brain cells, but not in a large enough quantity to help fight diseases.

"The brain and the body are deficient in the machinery to make DHA; it has to come through our diet," said Fernando Gomez-Pinilla.

DHA strengthens synapses in the brain and enhances learning and memory. It is abundant in wild salmon and, to a lesser extent, in other fish and fish oil, as well as walnuts, flaxseed, and fruits and vegetables.

http://newsroom.ucla.edu/releases/fructose-alters-hundreds-of-brain-genes-which-can-lead-to-a-wide-range-of-diseases

Gut - Brain Axis



The multiple bidirectional routes of communication between the brain and the gut microbiota. These routes include the vagus nerve, the hypothalamic-pituitary-adrenal axis (HPA), cytokines produced by the immune system, tryptophan metabolism and production of short chain fatty acids.

Ted Dinan, Professor of Psychiatry at University College Cork and Professor John Cryan, Chair of the Department of Anatomy and Neuroscience at University College Cork. Picture: Clare Keogh

Prof John Cryan told the BBC: "We were very surprised that you could, by just taking microbiome samples, reproduce many of the features of a depressed individual in a rat."

For the rats, that was sugary water they could not get enough of, yet "when they were given the microbiome from a depressed individual, they no longer cared", says Prof Cryan.

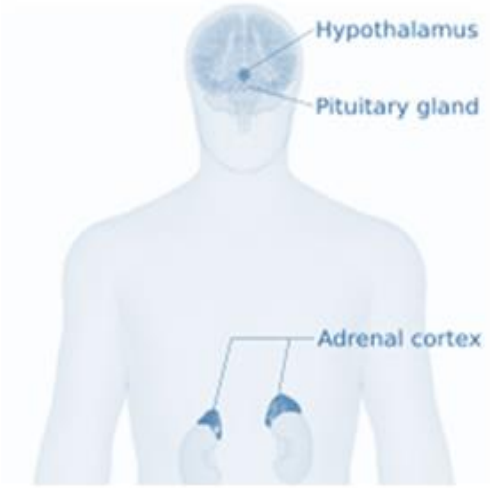
https://www.bbc.com/news/health-43815370

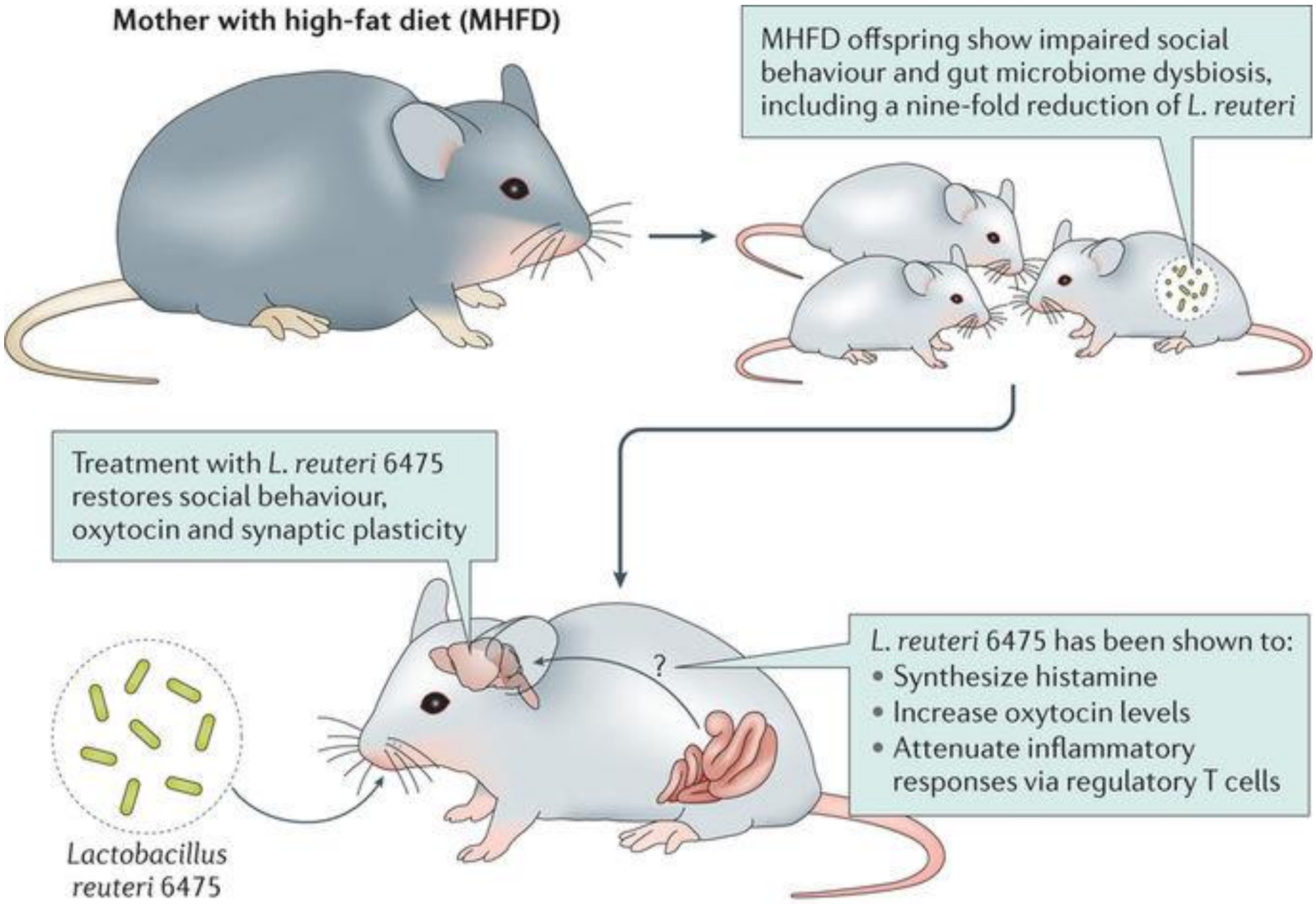
Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. https://www.ncbi.nlm.nih.gov/pubmed/27491067

The gut microbiota interacts with the host via neuroimmune, neuroendocrine and neural pathways. These pathways are components of the brain-gut-microbiota axis and preclinical evidence suggests that the microbiota can recruit this bidirectional communication system to modulate brain development, function and behaviour. The pathophysiology of depression involves neuroimmune-neuroendocrine dysregulation. However, the extent to which changes in gut microbiota composition and function mediate the dysregulation of these pathways is unknown. Thirty four patients with major depression and 33 matched healthy controls were recruited. Cytokines, CRP, Salivary Cortisol and plasma Lipopolysaccharide binding protein were determined by ELISA. Plasma tryptophan and kynurenine were determined by HPLC. Fecal samples were collected for 16s rRNA sequencing. A Fecal Microbiota transplantation was prepared from a sub group of depressed patients and controls and transferred by oral gavage to a microbiota-deficient rat model. We demonstrate that depression is associated with decreased gut microbiota richness and diversity. Fecal microbiota transplantation from depressed patients to microbiota-depleted rats can induce behavioural and physiological features characteristic of depression in the recipient animals, including anhedonia and anxiety-like behaviours, as well as alterations in tryptophan metabolism. This suggests that the gut microbiota may play a causal role in the development of features of depression and may provide a tractable target in the treatment and prevention of this disorder.

The most consistently demonstrated abnormality in depressed patients is hypothalamic–pituitary–adrenal (HPA) axis dysregulation, manifested as elevated cortisol and corticotropin releasing factor (CRF) and significant increases of pro-inflammatory cytokines.

Diet is one of the most important modifying factors of the microbiota-gut-brain axis.




Mother with high-fat diet (MHFD)
MHFD offspring show impaired social behaviour and gut microbiome dysbiosis, including a nine-fold reduction of L. reuteri
Treatment with L. reuteri 6475 restores social behaviour, oxytocin and synaptic plasticity
?
L. reuteri 6475 has been shown to:
• Synthesize histamine
• Increase oxytocin levels
• Attenuate inflammatory responses via regulatory T cells
Lactobacillus reuteri 6475

60 Females

Mice were obtained from Jackson Laboratories and were kept on a 12h light/dark cycle and had access to food and water ad libitum.

Females were placed on either a regular diet (RD) consisting of 13.4% kcal from fat, 30% kcal from protein, and 57% kcal from carbohydrates (Lab Diets, #5001) Or high fat diet (HFD) consisting of 60% kcal from fat, 20% kcal from protein, and 40% kcal from carbohydrates.

Maternal weight was measured weekly. Maternal total and fat mass were measured.

After eight weeks on diet, females were paired with C57Bl6/J adult males to produce subject offspring.

Resulting offspring were weaned at three weeks of age and all placed on RD.

After a month, these offspring showed behavioral deficits, such as spending less time in contact with their peers and not initiating interactions.

→

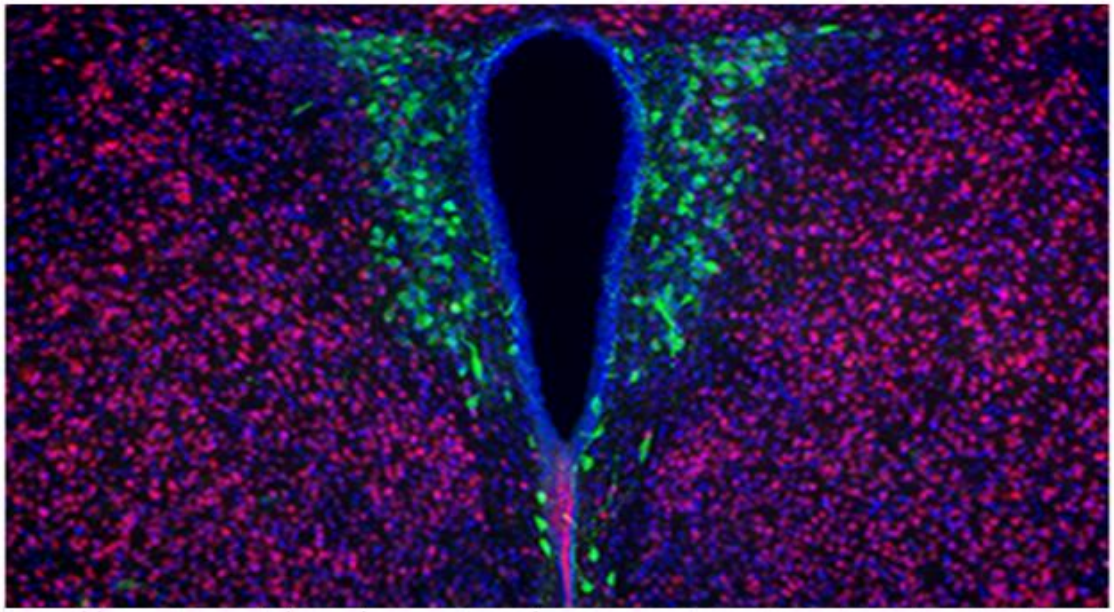
Lactobacillus reuteri was reduced more than nine-fold in the microbiome of mice born to mothers on the high-fat diet.

Species Whose Abundance Is Reduced in the Gut Microbiota of MHFD Offspring

Species of Interest	MRD Representation	MHFD Representation	Fold Change MRD/MHFD
Lactobacillus reuteri	7.49 ± 3.0	0.879 ± 0.21	9.24 ± 0.65
Parabacteroides distasonis	0.00709 ± 0.0055	0.00126 ± 0.0011	5.63 ± 1.17
Helicobacter hepaticus	7.35 ± 2.4	2.58 ± 1.3	2.84 ± 0.61
Bacteroides uniformis	5.49 ± 2.2	2.07 ± 0.78	2.65 ± 0.56
Olsenella unclassified	0.230 ± 0.064	0.121 ± 0.031	1.90 ± 0.38
Collinsella unclassified	0.0866 ± 0.031	0.0494 ± 0.016	1.75 ± 0.48
Bifidobacterium pseudolongum	19.4 ± 3.3	11.3 ± 2.4	1.71 ± 0.27
Lactobacillus johnsonii	24.5 ± 6.2	17.1 ± 5.2	1.43 ± 0.40

Among these, *L. reuteri* was the most drastically reduced (> 9-fold) in MHFD microbiota population, compared to the MRD microbiota.

https://www.sciencedirect.com/science/article/pii/S0092867416307309



https://www.bcm.edu/news/neuroscience/species-gut-bacteria-autism-related-behavior

Researchers showed that while the number of oxytocinergic cells (green) are reduced in the brains of maternal high-fat diet offspring, treatment with Lactobacillus reuteri increases their number.

Oxytocin Levels are reduced in the Hypothalamus of MHFD Offspring.

Mesolimbic Dopamine Reward System Function is Impaired in MHFD Offspring.

Brain regions that respond to naturally rewarding stimuli, including the ventral tegmental area (VTA) and the nucleus accumbens (NAc), are crucially involved in social behaviors .

"We cultured a strain of *L. reuteri* originally isolated from human breast milk and introduced it into the water of the high-fat-diet offspring. We found that treatment with this single bacterial strain was able to rescue their social behavior," Buffington says.

Other ASD-related behaviors, such as anxiety, were not restored by the reconstitution of the bacteria.

L. reuteri-treatment enhances oxytocin levels in the PVN of MHFD mice and direct oxytocin-treatment normalizes the social behavior of MHFD offspring . Although the precise mechanism by which *L. reuteri* promotes oxytocin in the brain remains to be determined, we favor the idea that the vagus nerve (Davari et al., 2013) could be the main pathway of communication between the gut/*L. reuteri* and changes in oxytocin in the PVN.

Researchers explain how oxytocin affects the brain. Some of the clearest evidence emerged from a team led by neurogeneticist Daniel Geschwind of the University of California, Los Angeles.

The group showed that mice that lacked a working copy of the Cntnap2 gene — which has been implicated in a small subset of human autism cases — had fewer oxytocin-containing neurons in the hypothalamus and socialized less with other mice than did control mice. After receiving doses of oxytocin every day for two weeks, the mice behaved normally again.

Published 24 June 2015

https://www.nature.com/news/neuroscience-the-hard-science-of-oxytocin-1.17813

CNTNAP2

Contactin-associated protein-like 2 is a protein that in humans is encoded by the *CNTNAP2* gene. Since the most recent reference human genome GRCh38, CNTNAP2 is the longest gene in the human genome.

Wikipedia

Lactobacillus reuteri (*L. reuteri*)

Published online 2018 Apr 19. doi: [10.3389/fmicb.2018.00757]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5917019/

In humans, *L. reuteri* is found in different body sites, including the gastrointestinal tract, urinary tract, skin, and breast milk. The abundance of *L. reuteri* varies among different individuals.

Several beneficial effects of *L. reuteri* have been noted.

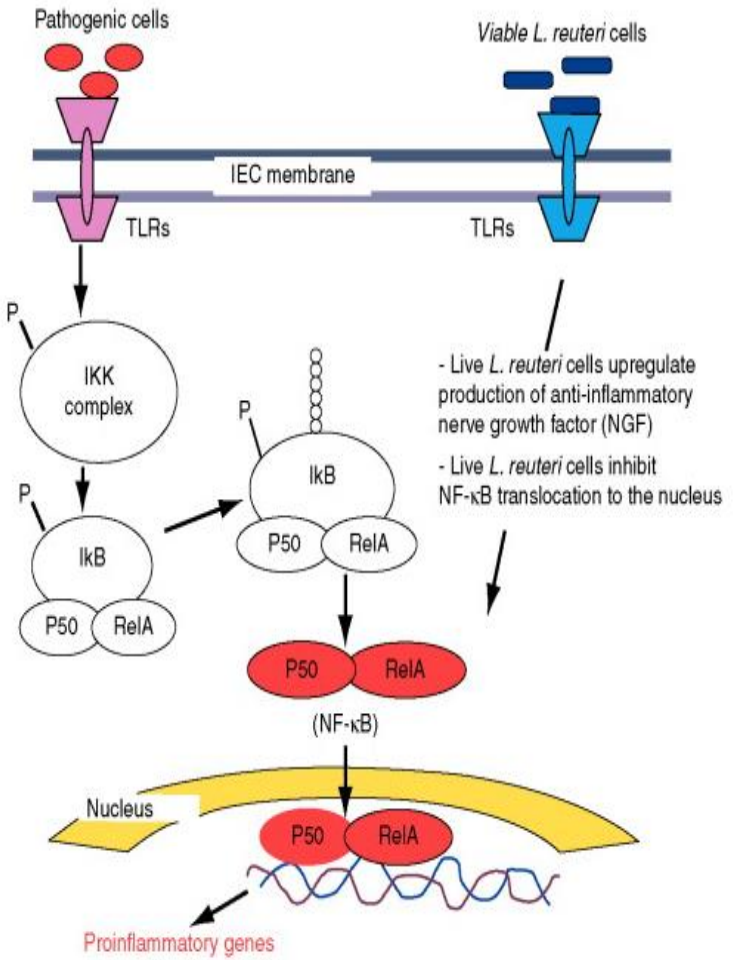
First, *L. reuteri* can produce antimicrobial molecules, such as organic acids, ethanol, and reuterin. Due to its antimicrobial activity, *L. reuteri* is able to inhibit the colonization of pathogenic microbes and remodel the commensal microbiota composition in the host.

Second, *L. reuteri* can benefit the host immune system. For instance, some *L. reuteri* strains can reduce the production of pro-inflammatory cytokines while promoting regulatory T cell development and function.

Third, bearing the ability to strengthen the intestinal barrier, the colonization of *L. reuteri* may decrease the microbial translocation from the gut lumen to the tissues. Microbial translocation across the intestinal epithelium has been hypothesized as an initiator of inflammation. Therefore, inflammatory diseases, including those located in the gut as well as in remote tissues, may be ameliorated by increasing the colonization of *L. reuteri*.

Notably, the decrease in the abundance of *L. reuteri* in humans in the past decades is correlated with an increase in the incidences of inflammatory diseases over the same period of time.

Direct supplementation or prebiotic modulation of *L. reuteri* may be an attractive preventive and/or therapeutic avenue against inflammatory diseases.



"A high fat diet can make you fat, but the fat is not the reason " BBC

https://betterbodychemistry.com/obesity/high-fat-diet/

Mouse dinners

When scientists conduct research using rodents, they don't spend time in the kitchen, preparing fancy meals for their little chargers They buy them "dinner", from the local "supermarket".

Companies that supply laboratory animal food, have a range of options. Most of the time, mice get fed, ordinary chow. Unless, the researchers want a fat mouse. **When a fat mouse is required, they more often than not, choose a high fat pellet.**

Are processed food

The high fat pellets are processed. The manufacturers have to follow a specific recipe, to create these special pellets. High fat pellets require the right mix of nutrients.

Typically the percentage fat is set at 60 %. Lard or vegetable oil can be used to achieve this figure. Next, the other macronutrients are added, the protein content is usually set at 20 %, leaving carbs to make up the last 20 %.

But, loading up the pellet with macronutrients is not enough, just like us, mice need to get their vitamins and minerals, to thrive. A dollop of vitamin and mineral mix, plus a pinch of choline and some sulphur amino acids, rounds off the nutritional ingredients.

The final thing typically added, is a smidgeon of fibre, frequently insoluble fibre is the fibre of choice.

BBC

Better Body Chemistry

Small things can make a big difference to your health
https://betterbodychemistry.com/obesity/high-fat-diet/

Laboratory mice enjoy their dinners. But, there is a difference between a highly processed dinner and something a bit more NATURAL.

Our team wondered if this mattered. So they fed batches of mice, different dinners.

Mice eating processed dinners Were fatter. The amount of fat in the dinner did impact the level of fatness , but mice eating a low fat (10 %) processed dinner were still a lot fatter than mice eating the less processed, ordinary chow. Oops. Fat was not the only factor, causing fatness.

Gut atrophy

When the team looked inside the mice, they found, mice eating the highly processed diets, had less intestine. Seriously, they had more fat and less intestine. When the animals intestine's were weighed and measured – they were significantly shorter and they weighed less.

What could cause the intestine to shrivel up like that ?

Lack of fibre

A series of further experiments found, the mice eating processed dinners, had the "wrong" crowd, living in their gut. The reason they weren't getting enough soluble fibre.

When the team supplemented the processed food with generous quantities of soluble fibre, the animal's guts looked normal.

Diet induced obesity

High fat diets used to induce obesity and obesity-related complications such as diabetes and metabolic syndrome typically have 40-60% of energy derived from fat. The diet tables below summarize relevant diet features for several Teklad custom research diets commonly used in rodent models.

https://www.envigo.com/products-services/teklad/laboratory-animal-diets/custom-research/diet-induced-obesity/

Commonly-used diet-induced obesity (DIO) Teklad rodent diets with 55-60% of calories from fat

Diet features	TD.06414 *stocked*	TD.93075 *dough*	TD.07011 *pellet*
Kcal/g	5.1	4.8	
Fat, % Kcal	60	55	
Fat Sources, % by weight	31% lard 3% soybean oil	27.4% vegetable shortening 1.6% corn oil	
Fatty acid profile, % total fat	37% saturated 47% monounsaturated 16% polyunsaturated	28% saturated, 30% trans 28% monounsaturated (cis) 14% polyunsaturated (cis)	
Sucrose, % by weight	12.1	9.6	
Notes	60F10S poster data Compare to D12492	Trans fat	
Example modifications	TD.08500 coconut oil TD.09766 milk fat		
Ingredient matched, low fat control diets*	TD.06416 (35% sucrose) TD.08806 (11% sucrose)	TD.93074 (21% sucrose) TD.120651 (7% sucrose)	
References	Mouse Rat	Mouse Rat	

TEMPLE UNIVERSITY

September 14, 2017

Researchers uncover mechanism behind calorie restriction and lengthened lifespan

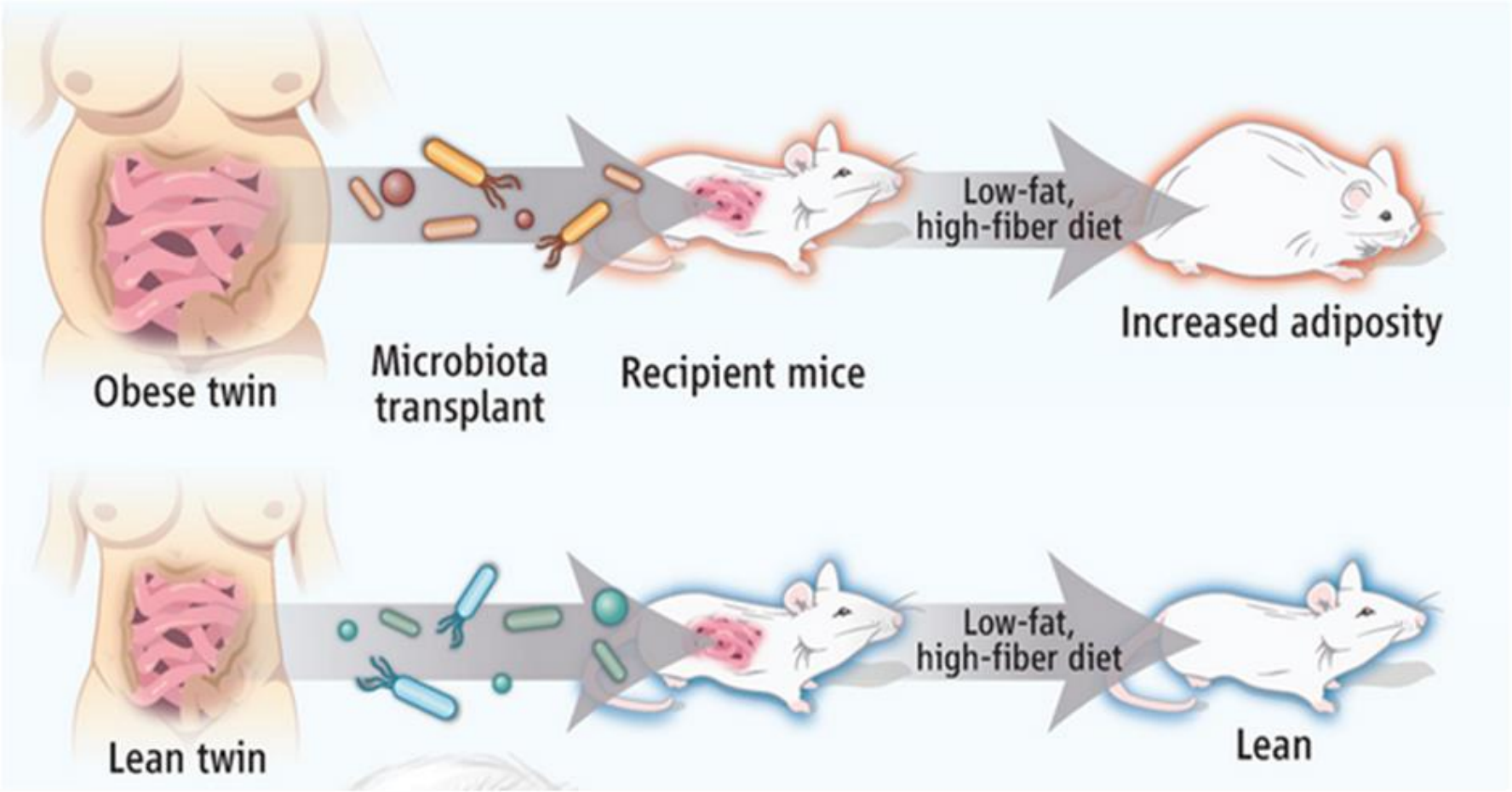
This study at Lewis Katz School of Medicine at Temple University (LKSOM) shows that the speed at which the epigenome changes with age is associated with lifespan across species and that calorie restriction slows this process of change, potentially explaining its effects on longevity.

Epigenetic drift, which is characterized by gains and losses in DNA methylation in the genome over time, occurs more rapidly in mice than in monkeys and more rapidly in monkeys than in humans, explains Jean-Pierre Issa. Chemical modifications such as DNA methylation control mammalian genes, serving as bookmarks for when a gene should be used. We examine methylation patterns on DNA in blood collected from individuals of different ages for each of three species – mouse, monkey, and human. Mice ranged in age from a few months to almost three years, monkeys from less than one year to 30 years, and humans from age zero to 86 years. The greater the amount of epigenetic change – and the more quickly it occurred – the shorter the species lifespan.

One of the strongest factors known to increase lifespan in animals is calorie restriction, in which calories in the diet are reduced while still maintaining intake of essential nutrients. To examine its effects, the researchers cut calorie intake by **40 percent** in young mice and by 30 percent in middle-aged monkeys. In both species, significant reductions in epigenetic drift were observed, such that age-related changes in methylation in old animals on the calorie-restricted diets were comparable to those of young animals.

Thanks to modern quantitative techniques, "we are able to show a striking slowing down of epigenetic drift as lifespan increases". Dr. Issa and colleagues propose a new mechanism – the slowing of epigenetic drift – to explain how calorie restriction prolongs life in animals. Greater amounts of epigenetic drift increase the risk of age-related diseases, including cancer. We propose the idea of modifying epigenetic drift as a way of modifying disease risk.

https://medicine.temple.edu/news/temple-researchers-uncover-mechanism-behind-calorie-restriction-and-lengthened-lifespan



Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice
Science 06 Sep 2013 Vol. 341, Issue 6150, 1241214 DOI: 10.1126/science.1241214
https://www.researchgate.net/publication/256452638_Gut_Microbiota_from_Twins_Discordant_for_Obesity_Modulate_Metabolism_in_Mice

We surveyed data collected from 21- to 32-year-old female twin pairs. ….Fecal samples were collected from each twin, frozen immediately after they were produced, and stored at –80°C. Each fecal sample was introduced, via a single oral gavage, into a group of 8- to 9-weekold adult male germ-free C57BL/6J mice (one gnotobiotic isolator per microbiota sample; each recipient mouse was individually caged within the isolator…4 mice per donor microbiota sample per experiment…. All recipient mice were fed, ad libitum, a commercial, sterilized mouse chow that was low in fat (4% by weight) and high in plant polysaccharides (LF-HPP) ... Fecal pellets were obtained from each mouse 1, 3, 7, 10, and 15 days post colonization and, for more prolonged experiments, on days 17, 22, 24, 29, and 35.

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

http://dx.doi.org/10.1126/science.1241214
Cite this article as V. K. Ridaura *et al.*, *Science* 341, 1241214 (2013).
DOI: 10.1126/science.1241214

C57BL/6 Background

http://science.sciencemag.org/content/sci/341/6150/1241214.full.pdf?keytype=ref&siteid=sci&ijkey=TUlCaqmJHSrdE

"The change in adipose mass of mice that received an obese co twin's fecal microbiota was significantly greater than the change in animals receiving her lean twin's gut community… Mice harboring the transplanted microbiomes from the obese twins exhibited higher expression of microbial genes involved in detoxification and stress responses; in biosynthesis of cobalamin; metabolism of essential amino acids (phenylalanine, lysine, valine, leucine, and isoleucine) and non essential amino acids (arginine, cysteine, and tyrosine)… Follow-up targeted tandem mass spectrometry (MS/MS)–based analysis of amino acids in sera obtained at the time mice were killed demonstrated significant increases in branched-chain amino acids (BCAA: Val and Leu/Ile)….. These specific amino acids, as well as the magnitude of their differences, are remarkably similar to elevations in BCAA and related amino acids reported in obese and insulin-resistant versus lean and insulin sensitive humans…. In contrast, the transplanted microbiomes from lean co-twins exhibited higher expression of genes involved in digestion of plant-derived polysaccharides [e.g., a-glucuronidase (EC 3.2.1.139), a-L-arabinofuranosidase (EC 3.2.1.55)]; fermentation to butyrate [acetyl-CoA C-acetyltransferase (EC 2.3.1.9), 3-hydroxybutyryl-CoA dehydrogenase (EC 1.1.1.157), 3-hydroxybutyryl-CoA dehydratase (EC 4.2.1.55), butyryl-CoA dehydrogenase (EC 1.3.8.1)] and fermentation to propionate [succinate dehydrogenase (EC1.3.99.1), phosphoenolpyruvate carboxykinase (EC 4.1.1.32), methylmalonyl-CoA mutase (EC 5.4.99.2)] … levels of butyrate and propionate were significantly increased and that levels of several mono- and disaccharides significantly decreased in animals colonized with lean compared with obese co-twin gut communities…"

"Cohousing Ob and Ln Animals prevents an Increased Adiposity Phenotype Because mice are coprophagic… the potential for transfer of gut microbiota through the fecal-oral route is high….Five days after gavage ,when each of the inoculated microbial consortia had stabilized in the guts of recipient animals, a mouse with the lean co-twin's culture collection was cohoused with a mouse with the obese co-twin's culture collection (abbreviated Lnch and Obch, respectively). All mice were 8-week-old C57BL/6J males. All were fed the same LF-HPPchow ad libitum…. Obch mice exhibited a significantly lower increase in adiposity…. higher levels of propionate and butyrate and lower levels of cecal mono- and disaccharides… there was significant invasion of components of the Lnch microbiota into the microbiota of Obch cage mates… The direction and success of invasion are shown in Fig. 2E... The most successful Lnch invaders were members of the Bacteroidetes (rank order of their invasion scores: Bacteroides cellulosilyticus, B. uniformis, B. vulgatus, B. thetaiotaomicron, B. caccae, Alistipesputredinis, and Parabacteroides merdae). Invasiveness exhibited specificity at the 97%ID OTU level (fig. S11)… Bacteroides in the Lnch community were efficient invaders of Obch communities because they were able to occupy unoccupied niches in Obch intestines. Note that increased representation of Bacteroidetes has been documented in several independent studies of the gut microbiota of conventionally raised lean mice compared with mice having genetic- or diet-induced obesity…"

The right ingredients

When the animals were fed a diet low in saturated fat and high in fruit and vegetables, the transfer of gut microbes from mice with the lean type to those with the obese type still occurred; however, when the mice were given a high-fat, low-vegetable diet this did not happen, and mice with the obese-type bacteria gained weight. "There's an intricate relationship between our diet and how our gut bugs work," says Gordon. "You have to have the right ingredients."

Food Sources of Short-Chain Fatty Acids

https://www.healthline.com/nutrition/short-chain-fatty-acids-101#section2

Eating a lot of fiber-rich foods, such as fruits, vegetables and legumes, is linked to an increase in short-chain fatty acids. One study of 153 individuals found positive associations between a higher intake of plant foods and increased levels of short-chain fatty acids in stools.

The following types of fiber are best for the production of short-chain fatty acids in the colon:

Inulin: From artichokes, garlic, leeks, onions, wheat, rye and asparagus.

Fructooligosaccharides (FOS): FOS are found in various fruits and vegetables, including bananas, onions, garlic and asparagus.

Resistant starch: From grains, barley, rice, beans, green bananas, legumes and potatoes that have been cooked and then cooled.

Pectin: Good sources of pectin include apples, apricots, carrots, oranges and others.

Guar gum: Can be extracted from guar beans, which are legumes.

Some types of cheese, butter and cow's milk also contain small amounts of butyrate.

Nouvelles preuves des bénéfices des fibres

Jan 30, 2018

Cette étude démontre que l'inuline fermentescible restaure la santé intestinale et permet de protéger des souris contre le syndrome métabolique induit par un régime riche en graisses. L'inuline fermentescible restaure les niveaux de bonnes bactéries, en augmentant la production de cellules épithéliales intestinales et en restaurant l'expression de la protéine interleukine-22 (IL-22). L'IL 22 empêche les bactéries du microbiote intestinal d'envahir les cellules épithéliales. De plus avec l'inuline, la taille des cellules graisseuses est diminuée, les taux de cholestérol abaissés et la dysglycémie réduite.

Les inulines sont un mélange de polysaccharides produit naturellement par de nombreux types de plantes. Elles appartiennent à une classe de fibres alimentaires appelées fructanes. L'inuline est utilisée par certaines plantes comme moyen de stockage de l'énergie que l'on retrouve généralement dans les racines ou les rhizomes. La plupart des plantes synthétisant et stockant de l'inuline n'accumulent pas d'autres matériaux énergétiques tels que l'amidon.

À la différence de l'amidon, l'inuline n'est pas digestible par les enzymes de l'intestin humain (amylases) et est considérée comme une fibre alimentaire soluble. L'inuline atteint donc le côlon intacte où elle est utilisée par la flore intestinale qui la métabolise, avec libération de quantités importantes de dioxyde de carbone, d'hydrogène et/ou de méthane : elle est ainsi considérée comme un prébiotique, au sens qu'elle stimule le développement des bactéries de la flore intestinale.

Les fibres solubles

Les fibres solubles forment un gel lorsque mélangées à l'eau et peuvent contribuer à abaisser le cholestérol sanguin. De plus, elles agiraient comme un filtre au niveau de l'intestin pour ralentir l'absorption des glucides. Il est nécessaire de consommer une très grande quantité de fibres, et ce, tous les jours, pour améliorer le contrôle glycémique.

Psyllium et céréales enrichies (ex. : All Bran Buds de Kellogg's)
Céréales et son d'avoine
Légumineuses
Fruits riches en pectine (pomme, orange, pamplemousse, fraise, poire, etc.)
Légumes (aubergine, gombo, asperge, haricots et pois verts, choux de Bruxelles, carottes, etc.)
Orge

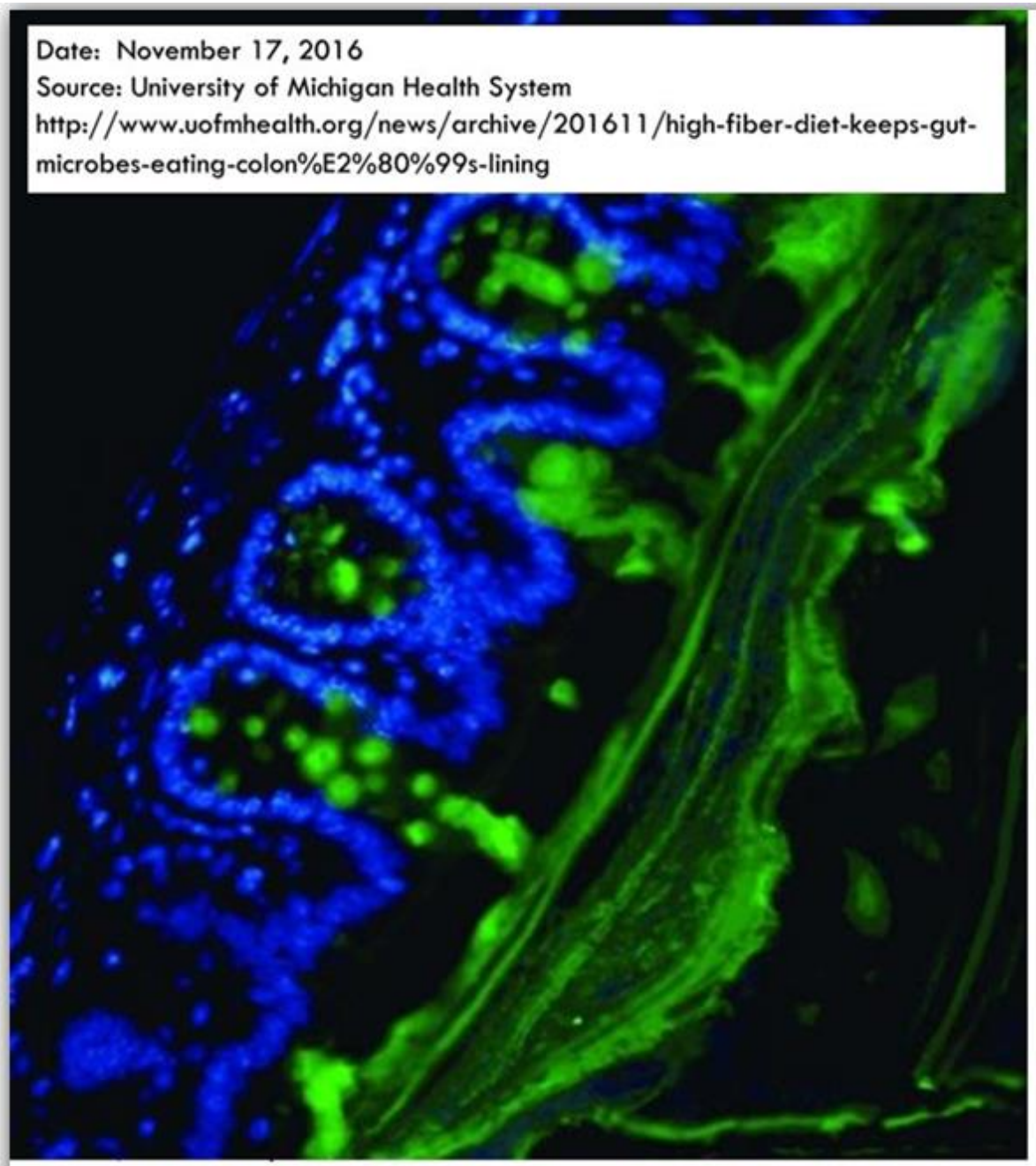
https://www.diabete.qc.ca/fr/vivre-avec-le-diabete/alimentation/alimentation-et-nutriments/les-fibres-alimentaires

Les fibres insolubles

Elles agissent comme des petites éponges dans l'intestin : en se gorgeant d'eau, elles augmentent le volume des selles et aident à régulariser la fonction intestinale. Comme elles ralentissent la digestion, elles favorisent la satiété, ce qui contribue au contrôle de l'appétit et du poids.

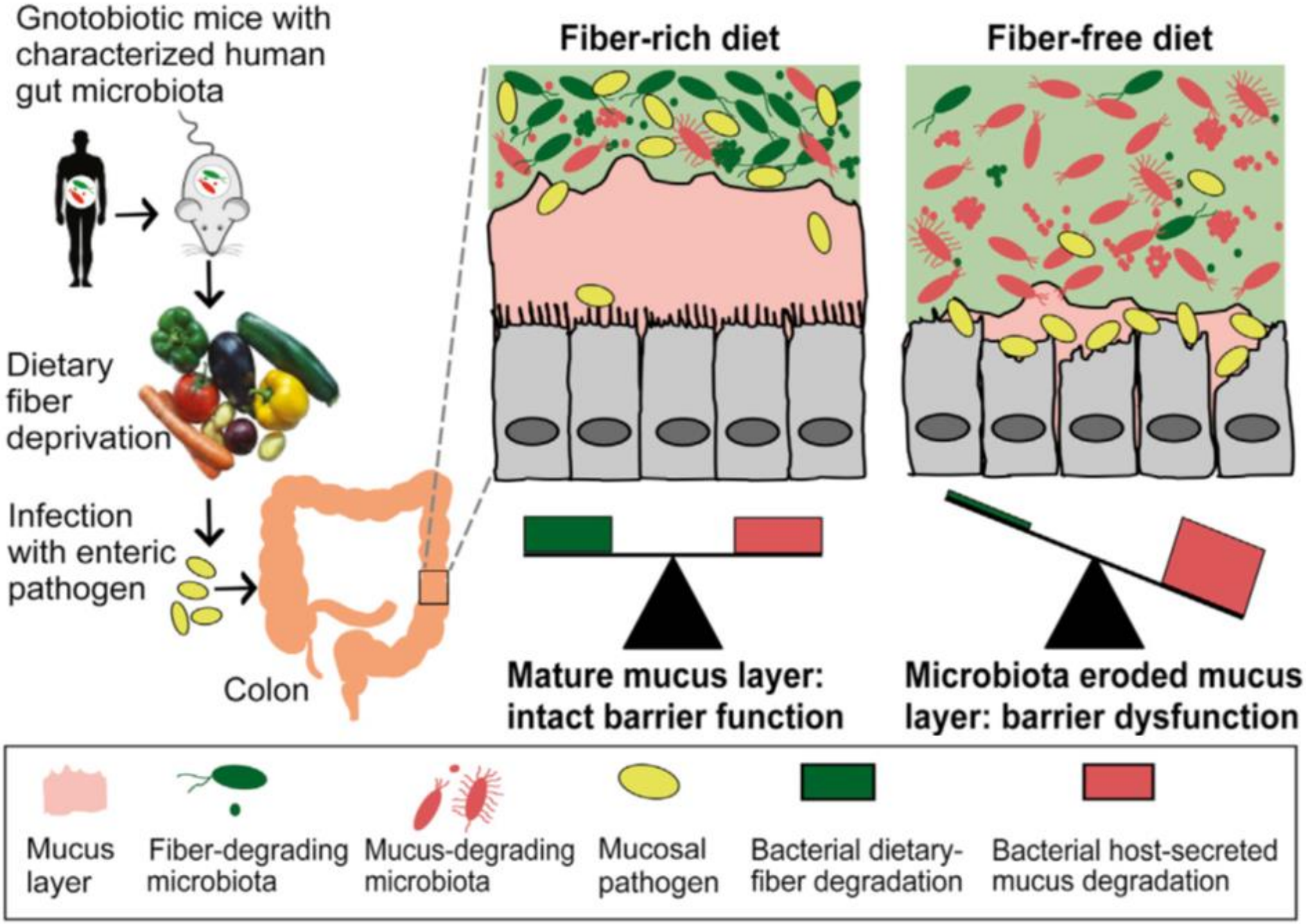
Céréales et son de blé
Aliments à base de grains entiers
Légumes et fruits
Noix et graines
Légumineuses (haricots rouges, lentilles, pois chiches, etc.)

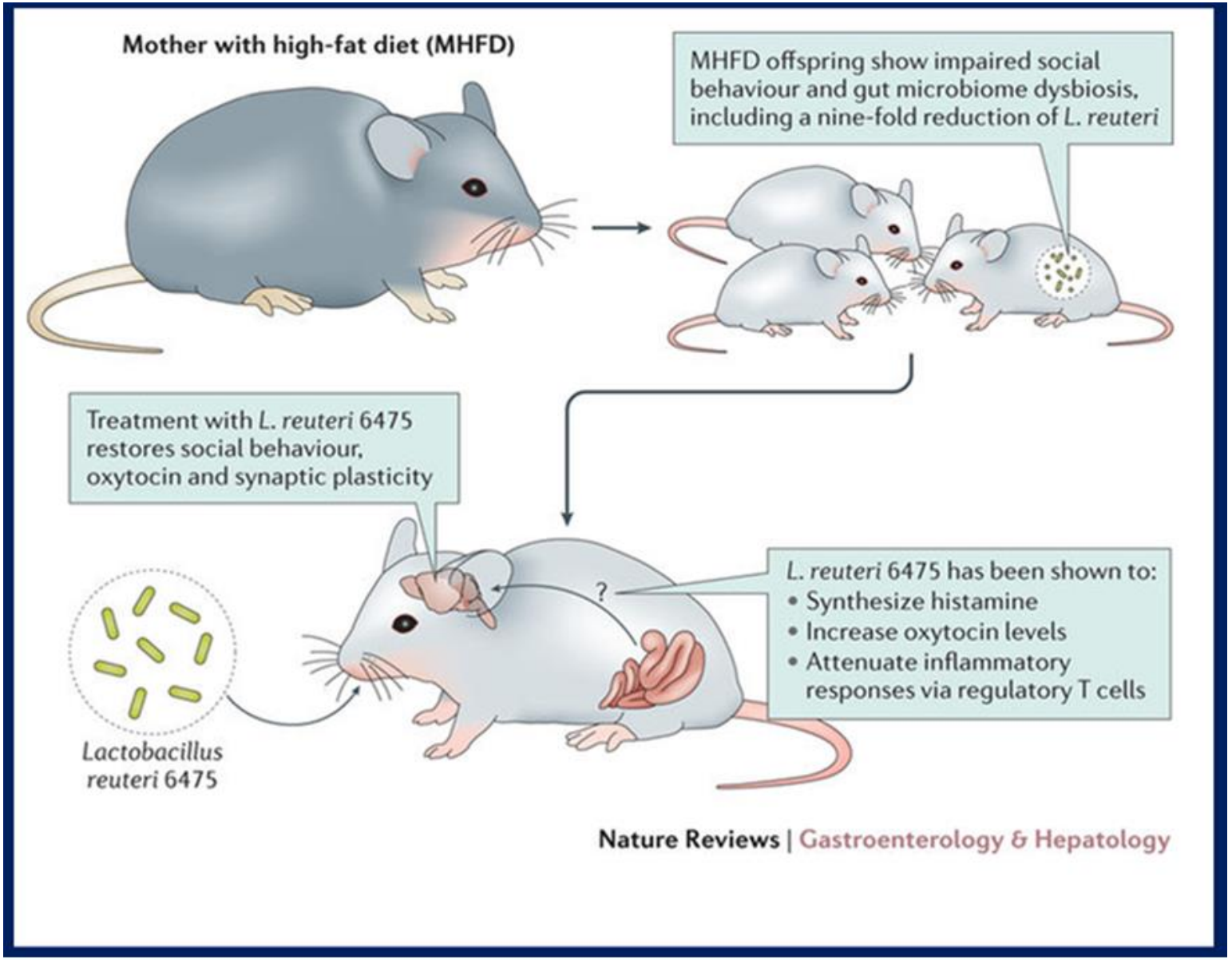
Date: November 17, 2016
Source: University of Michigan Health System
http://www.uofmhealth.org/news/archive/201611/high-fiber-diet-keeps-gut-microbes-eating-colon%E2%80%99s-lining



A thick mucus layer, generated by the cells of the colon's wall, provides protection against invading bacteria and other pathogens. This image of a mouse's colon shows the mucus (green) acting as a barrier for the "goblet" cells (blue) that produce it

High-fiber diet keeps gut microbes from eating the colon's lining, protects against infection, animal study shows


Gnotobiotic mice with characterized human gut microbiota
Dietary fiber deprivation
Infection with enteric pathogen
Colon
Fiber-rich diet
Fiber-free diet
Mature mucus layer: intact barrier function
Microbiota eroded mucus layer: barrier dysfunction
Mucus layer
Fiber-degrading microbiota
Mucus-degrading microbiota
Mucosal pathogen
Bacterial dietary-fiber degradation
Bacterial host-secreted mucus degradation



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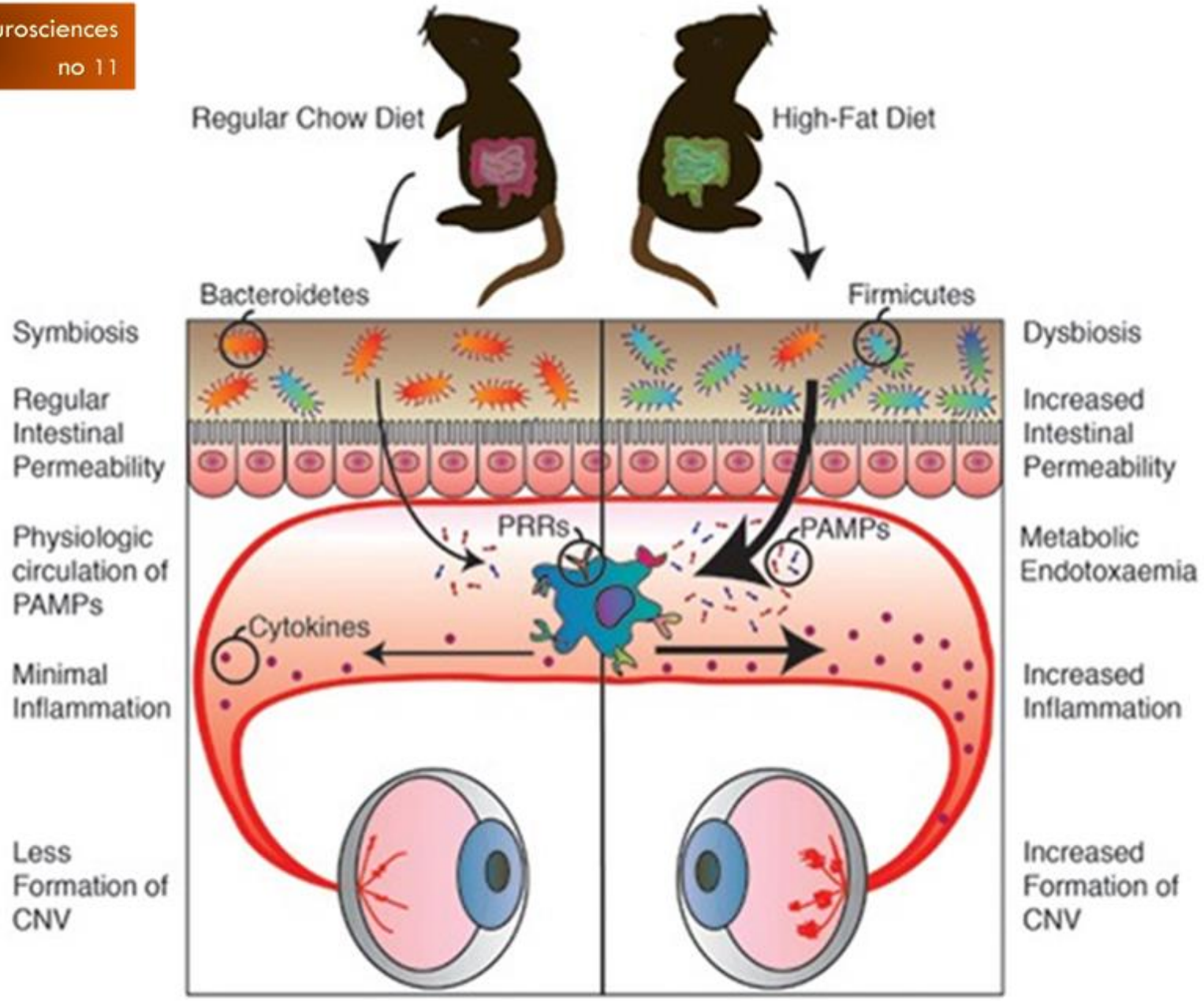

https://nouvelles.umontreal.ca/en/article/2016/11/15/microbes-in-your-gut-influence-major-eye-disease/

https://onlinelibrary.wiley.com/doi/full/10.15252/emmm.201606531