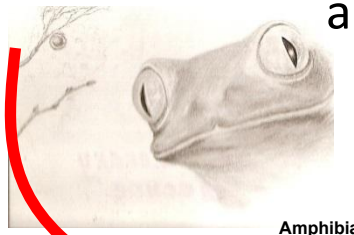
Neuropsychomodulating action of microbiota

Prof. Y.P. Uspenskiy

Microbes on Earth appeared 4.5 billion years ago!

Fish (440 millions years)

Approximately 1.5 billion years ago, there was a transition from small prokaryotic cells to large eukaryotic cells, similar to the cells of higher animals



Amphibians

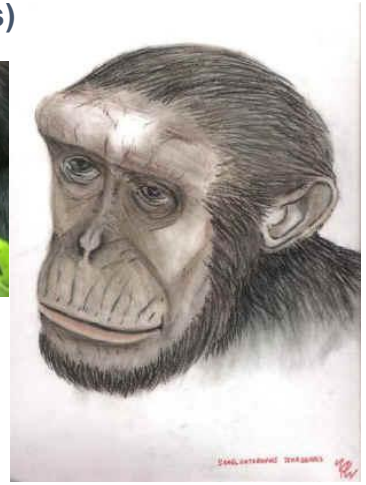
(400 million years)

Reptiles (300-320 million years)

Birds (220-240 million years)

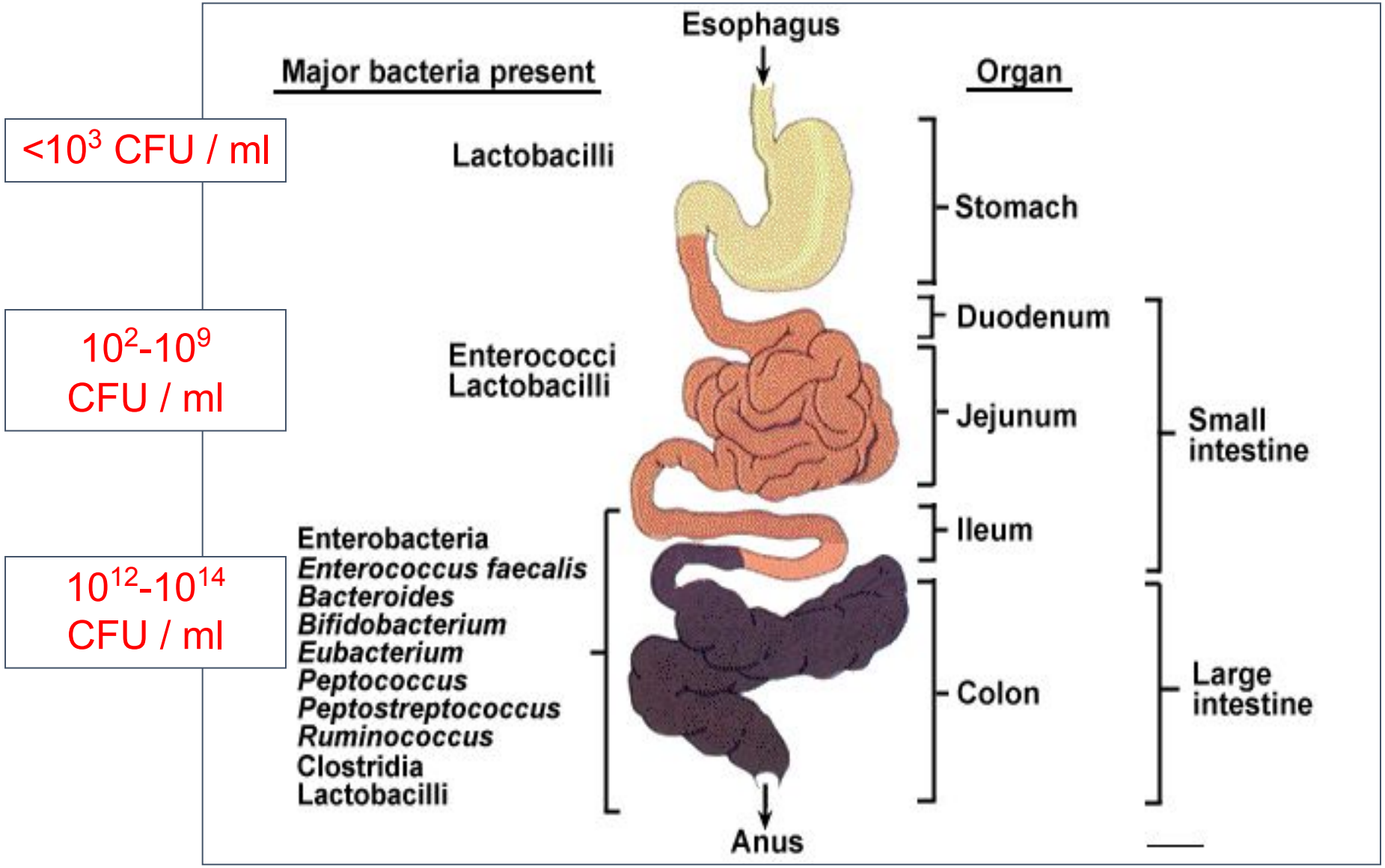
Mammals (200-250 million years)

Higher primates(38-25 million years)

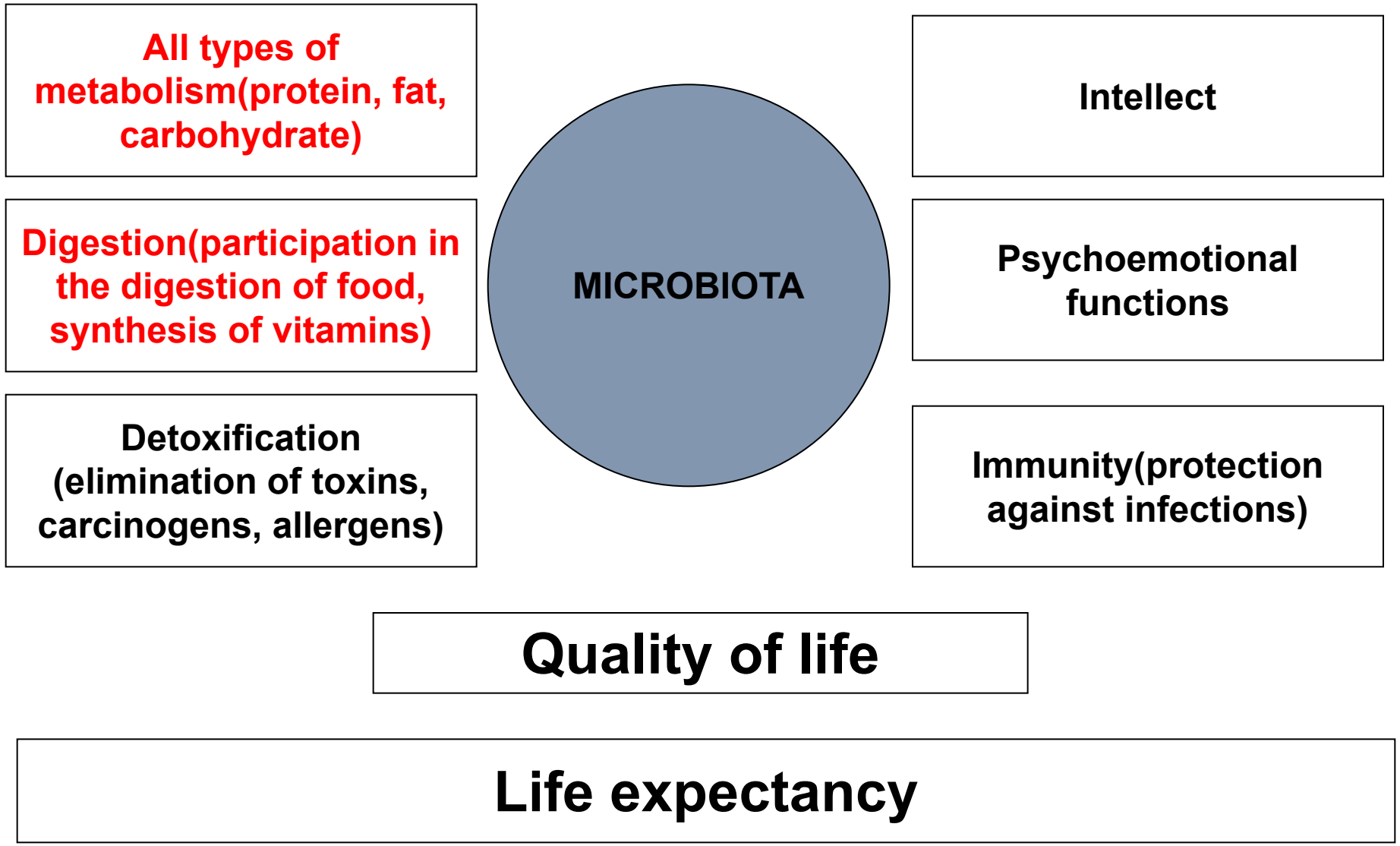


Prohuman (8 million years)

Microflora of gastro-intestinal tract



Main effects of the microbiota on humans

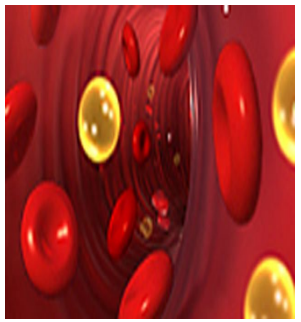


Known effects of some low-molecular-weight metabolites synthesized by the intestinal microflora

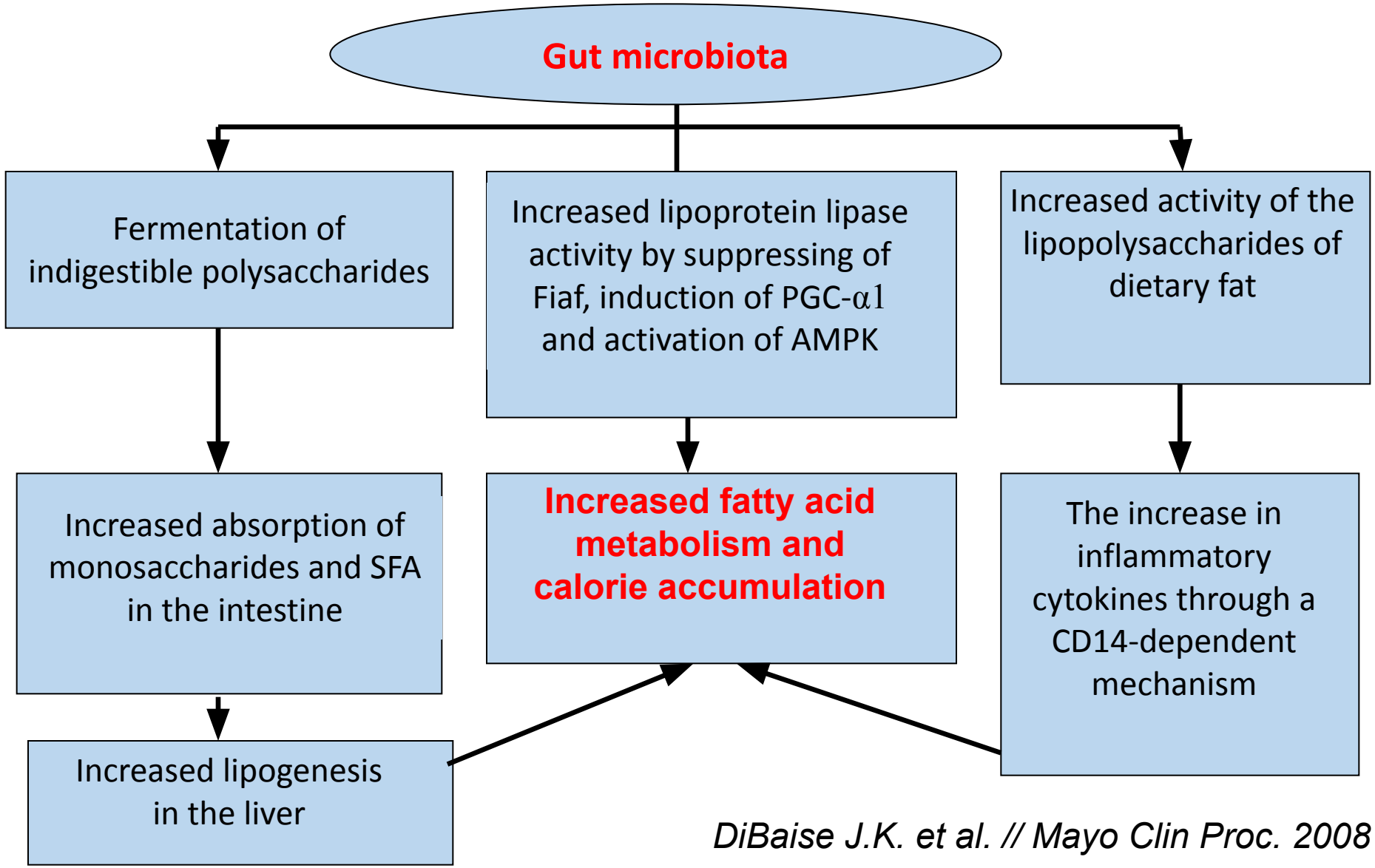
Metabolites	Effects
Butyric acid (butyrate)	energy supply of the epithelium; maintaining ion exchange; influence on epithelial differentiation and proliferation
Propionic acid (propionate)	antibacterial action; blocking the adhesion of pathogens to the epithelium; substrate of gluconeogenesis; induction of insulin secretion
Acetic acid (acetate)	the increasing of the local immune system; the substrate of lipogenesis
Isovaleric, isocaproic acids	induction of insulin secretion
Nitric oxide (NO)	regulation of intestinal motor activity; anti-apoptotic effect; regulation of vascular tone; antioxidant effect
Histamine, serotonin	regulation of secretory and motor activity of the digestive tract; mediators of inflammatory reactions; influence on vasomotor reactions, microcirculation

Participation of intestinal microflora in the metabolism of cholesterol

- transformation of Cholesterol in the gut-synthesis of coprostanol and neutral sterols
- inhibition of cholesterol synthesis in the liver (propionate)
- participation in the metabolism of steroid molecules - bile acids, hormones



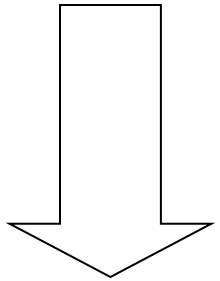
Mechanisms of influence of intestinal microflora on the development of obesity



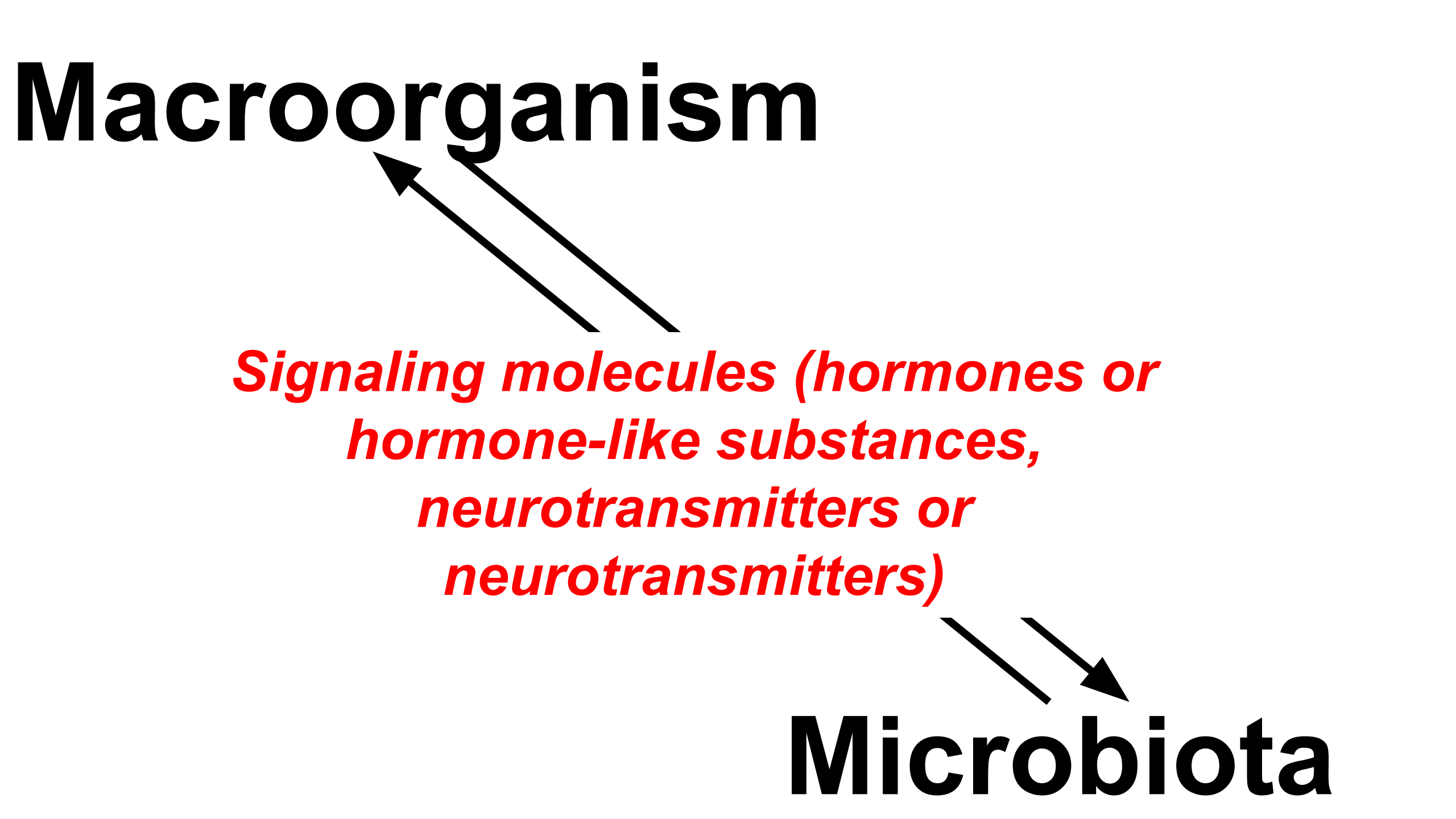
DiBaise J.K. et al. // Mayo Clin Proc. 2008

The microbiome is involved in the formation of metabolic syndrome, including through the modulation of human behavior, affecting the risks of developing so-called deviant (addictive, deviant, risky) behavior.

The microbiota is a source of neurotropic metabolites (GABA, glutamate, serotonin, histamine, peptides)



Neuropsychomodulating action

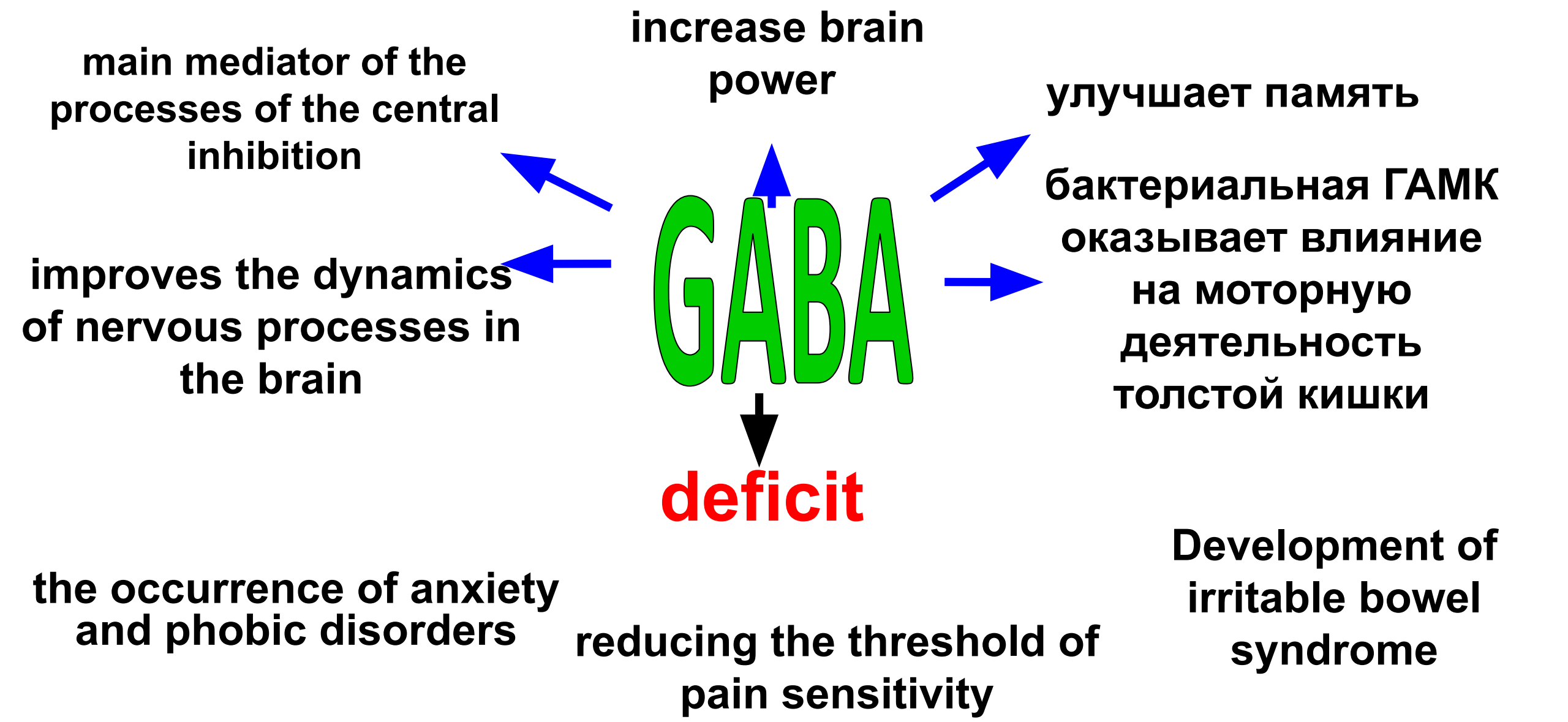

Macroorganism
Signaling molecules (hormones or hormone-like substances, neurotransmitters or neurotransmitters)
Microbiota

Microbial endocrinology is a biological field that emerged at the intersection of interests in Endocrinology and Microbiology

Lyte M., 1993

Gamma-aminobutyric acid (GABA)

(Produced by the symbiotic intestinal microflora, Escherichia coli, Bacillus fragilis)



The biosynthesis of serotonin

Serotonin is formed from the aminoacid tryptophan by its sequential 5-hydroxylation by the enzyme 5-tryptophan-hydroxylase (resulting in 5-hydroxytryptophan, 5-GT) and then decarboxylation of the resulting 5-hydroxytryptophan by the enzyme tryptophan-decarboxylase.

The main amount (80-95%) of serotonin is formed in the intestines.

The body circulates up to 10 mg of serotonin.

Серотонин

(Вырабатывается Escherichia coli, Rhodospirillum red, Streptococcus faecalis, Candida guillermondii, kind of bacillus glossy, kind of bacillus subtle, Staphylococcus aureus, Enterococcus faecalis)

the problem of development of power relations (dominance and subordination), the formation of social status

«hormone of sociality»

termoregulation

coordination of motor activity of internal organs

5-HT

human emotions

maintaining the rhythm of sleep and wakefulness (together with melatonin)

Perception of pain stimulation

Suppressing of pain sensitivity in extreme situations

Changes in the level of ammonium in the blood of prisoners during their stay in prison

In prisoners, there is a change in the composition of the intestinal microbiome with a decrease in the representation of bifidobacteria and lactobacilli and an increase in the level of ammonium in the blood serum. This phenomenon is a potential biological risk factor for behavioral disorders in prisoners. These changes are associated with the nature of prisoners ' nutrition and the lack of dietary fiber.

Yunfend D. Bihavioural Neurology, 2015

Analysis of intestinal microbiota in mice with artificially induced alcohol dependence

In an experiment in mice with artificially induced alcohol dependence, the composition of the intestinal microflora changes with an increase in the content of Firmicutes and Clostridiales, an increase in the ratio of Firmicutes to bacteroids, and a decrease in the content of Ruminococcus. In parallel, the severity of anxiety-depressive manifestations increases, the immune response and carbohydrate metabolism are disrupted.

W.Guanhao et al. Front Microbiol, 2018

Digestive homeostasis, microbiome disorders and opioids

In an experiment in mice, under the influence of opioids, epithelial intercellular contacts of the intestinal mucosa are damaged, the damaging effect of bile acid detergents on the mucous membrane increases, the metabolism of xenobiotics is disrupted, and the intestinal microflora shows a decrease in the level of bacteroids and bifidobacteria in the intestinal microbiome.

Fuyuan W. Toxicology Pathology, 2017

Microbiota disorders in individuals with emotionogenic eating behavior and food preferences in the form of a desire for sweet food

According to studies in China and Sweden, changes in the gut microbiota were recorded in obese individuals with emotional eating behaviors and food preferences in the form of a desire for sweet food in the form of an increasing loss of intestinal microbial diversity and specific taxonomic groups, such as Bifidobacteria and Verrucomicrobiae (akkermansia muciniphil is a representative of the latter phylogenetic class). Moreover, changes in the microbiota were more strongly correlated with diabetes mellitus type 2 (DM2) than with classic risk parameters for DM2, such as body weight, body mass index (BMI), waist circumference, or waist-to-hip ratio.

Qin J. Nature 2012, Karlsson F.H. Nature 2013

Disorders of the microbiota and neurogenic anorexia

In patients suffering from anorexia, in the composition of the gut microbiome with marked reduction of bacteroidetes and increasing the level of firmicutes.

M.Sjogren Anorexia and Bulimia nevrosa 2019

Smoking abstination leads to significant changes in the gut microbiota

In patients who quit Smoking in the intestinal microflora after 3 months, there is a decrease in the level of firmicut and an increase in the level of bacteroids.

American Pilot Study J.-S. Knick 2019

Coffee intake and gut microbiota

Consumption of 82.9 mg of caffeine per day (slightly more than a standard Cup of espresso) leads to positive changes in the composition of the intestinal microbiota in the form of increased level of Faecalibacterium Roseburia, which play a role in the development of anti-inflammatory mechanisms and reduced Erysipelatoclostridium (E. Ramosum), which are associated with metabolic syndrome and diabetes mellitus.

American school gastroenterology Huston 2019

Hystory of Post-infectional irritable bowel symdrome (PI-IBS)

- For the first time in 1950, G. T. Stewart described that24-32% of patients who have had acute intestinal infection develop an IBS-like syndrome within 3 months.

Stewart G.T., 1950

- In 1961, N. A. Chaudhary and S. C. Truelove described PI-IBS after studying 130 cases of "irritable bowel syndrome", they identified 26% of patients who had IBS as a result of dysentery.

Chaudhary N. A., Truelove S. C., 1962.

Clinical and laboratory criteria for PI-IBS
(data drom CSRI of gastroenterology, Moscow

- ✔ The reference in the history of acute intestinal infection, prior to the disease
- ✔ Detection of acute intestinal infection markers in the patient's biological environments
- ✔ Signs of dysbiosis in bacterial cultures of feces
- ✔ Increased bacterial growth in the small intestine
- ✔ Reducing the tension of the immune system
- ✔ Positive effect of therapy with biologically active drugs, pre-and probiotics

Ручкина И.Н., 2005 (Ruchkina I.N., 2005)

PI-IBS and tome factor

- 24-32 % of patients who have had acute intestinal infection have IBS-like syndrome within 3 months.

Stewart G.T., 1950.

- 7-33% of patients develop an IBS-like condition between 3-4 months and 6 years after infection.

McKendrick M.W., 1994; Neal K.R., 1997; Spiller R.C., 2000.

- The majority of people who develop acute bacterial diarrhea, spontaneous disappearance of symptoms occurs within < 5 days, but some patients develop non-specific intestinal symptoms, which may occur within the next 6 years.

Neal K. R., Barker L., Spiller R. C., 2002.

- After acute gastroenteritis (C. jejuni, Escherichia coli 0157:H7) in 15.4% of patients symptoms persisted for up to 8 years.

Marshall J.K., 2010.

PI-IBS and ethiology factor

- PI-IBS developes in **4–32% of patients after bacterial gastroenteritis** (5-10%) as a response to non-specific infections caused by various intestinal pathogens, such as Campylobacter (25% of cases), Salmonella, diarrheal strains of Escherichia coli, Shigella, Entamoeba histolytica, Yersinia, Cryptosporidium, Legionella.

Spiller R.C., Campbell E., 2006; Spiller R.C., Jenkins D., Thornley J.P. et al., 2000;

Gwee K.A., Collins S. M., Read N. W., 2003; Wang L.H., Fang X.C., Pan G.Z., 2004;
Triantafillidis J.K., Peros G,. 2007.

- ***Acute gastroenteritis (C. jejuni, Escherichia coli 0157:H7***) the frequency for mild severity is 27%, and confirmed cases are 36%.

Marshall J.K., 2006.

- **bacterial gastroenteritis** – OR 2.2

Törnblom H., 2007.

Excessive bacterial growth in the small intestine and motility

Table 1 Demographic characteristics of patients with a new diagnosis of IBS (*n* = 97)

Demographic characteristics	*n*	Breath test at screening	
		Positive (*n* = 54)	Negative (*n* = 43)
Sex (M/F, mean ± SD)	40/57 (40.7 ± 16.2)		
IBS variants *n* (%)			
Chronic diarrhoea	31 (31.9)	19 (35.2)	12 (27.9)
Stipsis	20 (20.6)	11 (20.4)	9 (20.9)
Alternated stipsis/diarrhoea	46 (47.5)	24 (44.4)	22 (51.2)
Symptoms score			
Chronic diarrhoea	2.2 ± 0.8	2.2 ± 0.7	2.1 ± 0.6
Stipsis	2.3 ± 0.9	2.4 ± 0.8	2.1 ± 0.9
Alternated stipsis/diarrhoea	2.0 ± 1.2	2.3 ± 0.9	1.7 ± 0.6[a]

[a]Statistically significant difference between groups, $P = 0.019$.

Peralta S. et al. , 2009

Mild inflammation of the colon and increased intestinal permeability in IBS

- The association of polymorphisms in the IL-4, IL-6, IL-10, and TNF-α genes encoding proinflammatory interleukins with the development of PI-IBS was revealed;
- Increased IL-1B expression in rectal biopsy in patients withPI-IBS, compared to those who had infectious enteritis without subsequent PI-IBS.

Gwee K. A., Collins S. M., Read N. W. et al., 2003.

- increased IL-1B in patients with PI-IBS after Shigella infection compared to patients without IBS.

Marshall J. K., Thabane M., Garg A. X. et al., 2004;

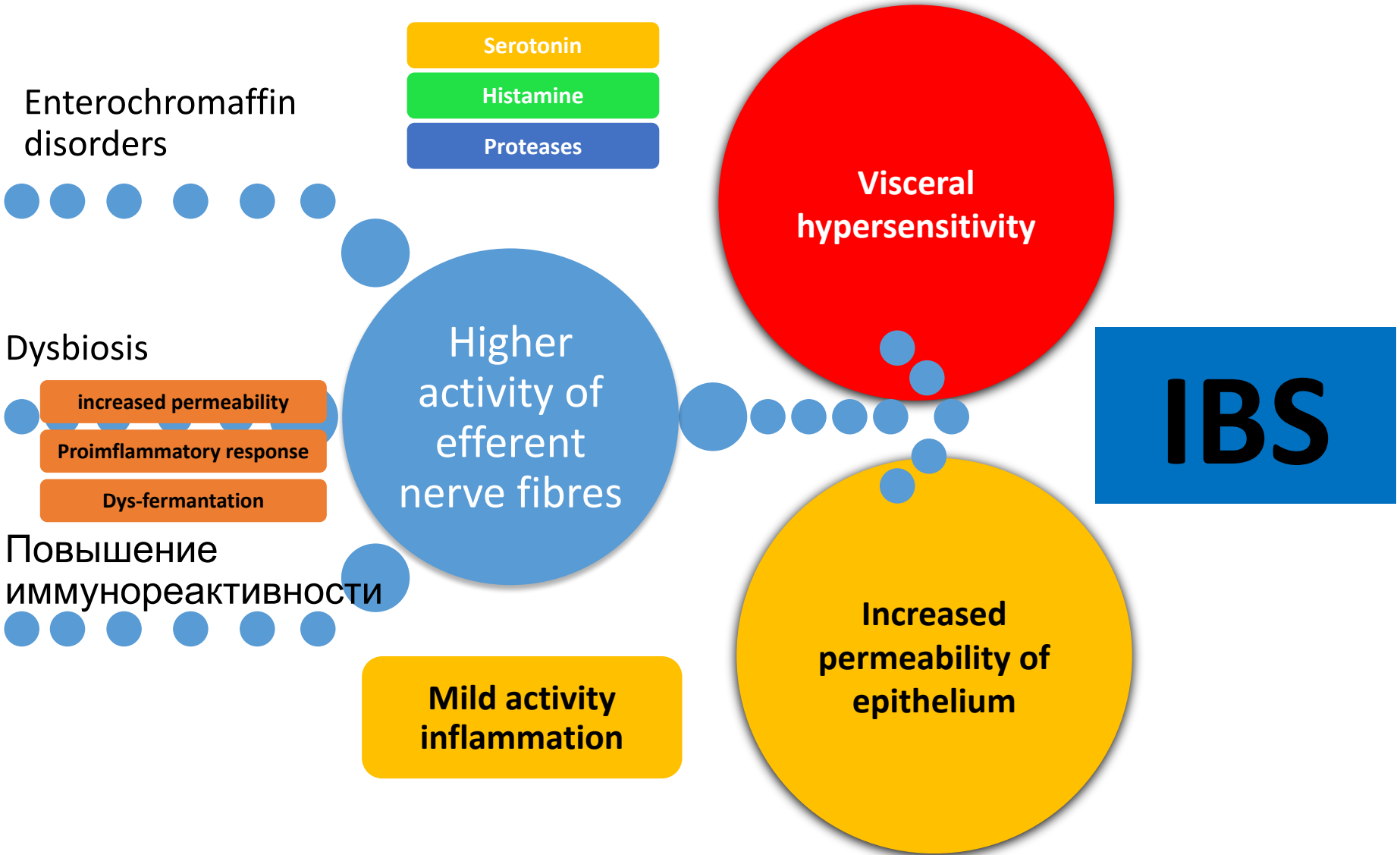
Wang L. H., Fang X. C., Pan G. Z., 2004.

- three genes have been identified — TLR9, CDH1, and IL6 that are associated with the development of PI-IBS.

Villani A., Lemire M., Thabane M., 2008

- a single-nucleotide substitution was found in the promoter of the CDH1 gene encoding a transmembrane glycoprotein that regulates intercellular adhesion.

Pathological cascade



Features of the clinic of PI-IBS

- In patients with PI-IBS with isolated presence of shigell antibodies, abdominal pain was more often localized mainly in the left iliac region (in the projection of the sigmoid colon), and increased before defecation. Constipation and false urge to defecate were common.
- Patients with Yersinia antigens more often complained of loose stools, pain mainly in the lower right quadrant of the abdomen (in the ileocecal region), which decreased after stool.
- Patients with Salmonella or C. jejuni antigens complained of spilled abdominal pain, decreasing after stool, diarrhea with mucus.
- Patients with mixed infection were concerned about diarrhea, dull pain around the navel or in the projection of the colon, which decreased after the act of defecation, and weight loss.
- In patients with enteroviruses detected in the feces, the clinical picture was characterized by frequent liquid copious stool with mucus, spilled abdominal pain of a cramping nature, mainly before the stool, and some weight los.
- In patients with PI-IBS with bacterial growth in the small intestine, the clinical picture was characterized by severe diarrhea.

Meta-analysis of the effectiveness of probiotics in IBS

- Abdominal pain
  - Probiotics have positive effects, RR 1.96 (95%CI: 1.14-3.36; P = 0.01)
- Global symptom score
  - Probiotics have positive effects, 2.43 (95%CI: 1.13-5.21; P = 0.02)
- Вздутие, метеоризм, флатуленция
  - Probiotics have positive effects, -2.57 (95%CI: -13.05--7.92)

Didari T. et al. World J Gastroenterol. 2015 Mar 14; 21(10)

Recommendation of Russian gastroenterology association

4.2.5. *Пробиотики*

Лечебное действие различных пробиотиков при СРК подтверждено рандомизированными контролируемыми исследованиями и систематическим обзором Cochrane Database Уровень доказательности соответствует II категории, уровень практических рекомендаций – категории В [47–50]. Эффект от терапии следует оценивать не ранее чем через 4 недели от начала приема препарата в дозе, рекомендованной производителем. Доказана эффективность пробиотиков, содержащих такие микроорганизмы, как *B. infantis, B. animalis, B. breve, B. longum, L. acidophilus, L. plantarum, L. casei, L. bulgaricus, S. thermophilus.*

4.2.5. Probiotics

Treatment effect of probiotics base on randomized trials and systematic review Cochrane . Probiotics effect cam be estimated not early than 4 weeks after beginning of treatment. Probiotic with proved efficacy: B. infantis, B. animals, B. breve, B. longum, B. acidophilis, L. plantarum, L.casei, L. burgaricus, S. thermophilis

Effectiveness of probiotics in IBS

A meta-analysis of 16 randomized controlled trials found that most of them had methodological errors. There was some evidence for the effectiveness of Bifidobacterium infantis 35624 in two well-organized studies.

- Bifidobacterium infantis probiotic was significantly more effective than placebo in a 4-week controlled study of 362 patients with IBS*.
- 77 patients with IBS were randomly assigned to: those who consumed a milk powder drink with Lactobacillus salivarius UCC4331 or with Bifidobacterium infantis 35624, as well as those who consumed regular milk. Symptoms significantly decreased in the group treated with B. infantis. In addition, normalization of the IL-10/IL-12 ratio in blood serum was noted, which confirms a decrease in Pro-inflammatory activity associated with IBS**
- *Whorwell, PJ, Altringer, L, Morel, J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101:1581.
- ** O'Mahony, L, McCarthy, J, Kelly, P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005; 128:541.

И.И. Мечников писал , что многочисленные ассоциации микробов, населяющих кишечник человека, в значительной мере определяют его духовное и физическое здоровье, а кожа и слизистые покрыты в виде перчатки биопленкой, состоящей из сотен видов микробов

[Metchnikoff I., 1908].

I. Mechnikov wrote that numerous associations of microbes inhabiting the human gut largely determine its spiritual and physical health, and the skin and mucous membranes are covered in a glove-like biofilm consisting of hundreds of types of microbes

[Metchnikoff I., 1908]

Считал, что долголетие человека связано с удалением условно-патогенных микроорганизмов из кишечника и предложил проводить заселение пищеварительного тракта болгарской молочно-кислой палочкой- создан первый кисломолочный продукт — «Простокваша Мечникова».

He believed that human longevity is associated with the removal of opportunistic microorganisms from the intestines and proposed to colonize the digestive tract with Bulgarian lactic acid Bacillus-the first fermented milk product was created-"Mechnikov's Yogurt".

THANKS FOR YOUR ATTENTION!