Chapter

Dysbiosis of the Microbiota in Anorexia Nervosa: Pathophysiological Implications

Magnus Sjögren, Stein Frostad
and Kenneth Klingenberg Barfod

Abstract

Anorexia nervosa (AN) is a severe and often enduring condition of which the etiology is unknown. Studies on the gut microbiota in AN have found deviations from that of healthy individuals, which may imply a relation to pathophysiology, development and maintenance of the disorder via the gut-brain axis, which has been shown in other disorders. A narrative review of the gut microbiota studies in AN is presented. Several studies point to a dysbiosis in AN which may have implications for maintenance of a low body weight, immunological changes and a severely reduced food intake. An association may be found to clinical symptoms in AN. A pathophysiological model for disease is presented implying a role of the microbiota in maintenance of AN. Dysbiosis in AN may play an important role in the development and maintenance of AN.

Keywords: anorexia nervosa, feces, microbiota, species, biomarkers

1. Introduction

Anorexia nervosa (AN) is a serious and often enduring psychiatric condition. The hallmark features of AN are a phobia for weight gain, and for intake of fattening food, disturbance in body image, and often compensatory behaviors such as excessive exercise and purging, which overall leads to a reduction of energy intake relative to energy expenditure leading to low body weight. An increased risk of suicide and frequent potential life-threatening medical complications of several body organs contribute to AN having a high standardized mortality ratio of 5.2 [3.7–7.5] [1]. This is coupled with a high risk of enduring disease [2].

The weight loss is in some patients preceded by a depression, a trauma, gastrointestinal symptoms or an infection. But in a majority of patients there is no detectable psychiatric or somatic disorder preceding the weight loss. In children and adolescents with AN, family-based treatment as described by Lock and LeGrange is recommended [3] and if treatment is started shortly after debut of the disorder, the prognosis is fairly good. However, if treatment is delayed, the prognosis becomes worse [4]. In adults, individual eating-disorder-focused therapy (CBT-ED) is recommended [5]. With this treatment, drop-out rates are high and even with optimal treatment by well-trained therapists only 50% of the patients who start CBT-ED have good effect of the therapy [6, 7].
Considering the high mortality, high chronicity and lack of knowledge on the etiology of AN, there is an immense need for an improved understanding of the etiology and pathophysiology of the disease in order to find ways to better treatments. This knowledge would preferably explain both the routes into developing the disorder and mechanisms that serve to maintain it, and proposedly involve both biological and psychological factors, such that measures and biomarkers to follow the development and recovery from of the disease could be identified. Potential further benefits with biomarkers for AN may be guidance for risk stratification, treatment and target identification for novel treatments. The last few years have seen an increase in studies on the gut microbiota and its associated microbiome which might harbor trait biomarkers for AN.

The “microbiota” refers to the cumulative microorganisms, including Bacteria, Viruses, Archaea, Protists and Fungi, which populate a number of human tissues and biofluids including the skin, lungs, roal mucosa, saliva, and gastrointestinal tract, and the “microbiome” refers to the collective genomes of the present microorganisms [8]. There are more than 1000 ‘species-level’ phylotypes that coexist in a human [9], and the majority of these phylotypes are Bacteria, with Faecalibacterium prausnitzii, Roseburia intestinalis, and Bacteroides uniformis dominating in the adult microbiota found in feces samples [10]. The composition of the phylotypes is mostly consistent across individuals, albeit there may be a large variability with regard to relative composition and diversity of the included microorganisms, intra-individually depending on anatomical site and inter-individually at the same anatomical location. In addition, there are inter-individual variations at the same anatomical site.

The gut microbiota is critical for the development of the gut mucosal immunity [11, 12], and it is also involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [13], serotonergic neurotransmission [14], and signaling mechanisms affecting neuronal circuits involved in motor control and anxiety in mice [15]. This pathway has been named the gut-brain axis [16].

2. The gut-brain axis

The existence of the gut-brain axis is exemplified by irritable bowel syndrome (IBS) where more than half of the patients also suffer from mood disorders and for which antidepressants is one of the more common pharmaceutical treatments [17]. In IBS and other potential gut-brain axis disorders, cognitive alterations seem to be key features of the disorders [18]. These cognitive alterations might be induced by signal transduction from gut to the brain [18]. In addition, the existence is also shown by the effects of antibiotic exposure, which may lead to altered brain function such as anxiety, panic disorder, major depression, psychosis, and delirium which are usually described as side effects of antibiotic treatment [19]. Support for the latter comes also from studies in mice which have shown that an altered composition of the gut microbiota in adult mice, and an increased exploratory behavioral including hippocampal expression of Brain Derived Nerve growth Factor (BDNF) has been found after oral administration of non-absorbable antimicrobials [20], in contrast to intraperitoneal administration, which had no effect on behavior or BDNF levels.

Another area of evidence for the gut-brain-axis stems from dietary induction of changes in gut microbiota and linked psychopathological outcomes. For example, a high fat diet has been found associated with an altered microbial diversity and diminished synaptic plasticity [21, 22] but also increased vulnerability and anxiety-like behavior in the mice [23]. In addition, a diet high in sucrose also led to an altered microbial diversity associated with impaired development of spatial bias for
Dysbiosis of the Microbiota in Anorexia Nervosa: Pathophysiological Implications
DOI: http://dx.doi.org/10.5772/intechopen.85253

long term memory, short term memory, and reversal trainings [24]. Another strong evidence for the gut-brain axis comes from a study in mice exposed to a microbiome depletion and/or transplantation paradigm where microbiota, in a first step, was isolated from donors who were provided with either high fat diet or a controlled diet, and thereafter in a second step, transfused to mice who developed significant and selective disruptions in exploratory, cognitive, and also developed the stereotypical behavior following the high fat diet [25]. However, there are also evidence from studies where alcohol exposure, smoking habits, and disruptions in diurnal rhythm all have been shown to affect the microbiota composition.

There are also other evidence pointing to a reciprocal interaction from a study where a second generation antipsychotics, olanzapine, was exposed to rats and found to affect the composition of the microbiota, which also triggered an inflammatory response and weight gain [26, 27]. Furthermore, the exposure to antibiotics seemed to attenuate these physiological effects [28].

The microbiome has also been found to have been altered in various psychiatric conditions, or to affect its clinical expression, as well altered in rodent models for these disorders [29]. One example is major depressive disorder (MDD) where, for example, in germ-free mice (mice completely void of bacterial microbiota or derived molecules), there are both changes from comparable normal mice in the hypothalamic, pituitary, adrenal stress response, as well as altered levels of monoamines concentrations or their receptors [13–15, 20, 30]. Indirect evidence in MDD also comes from an increased serum antibody level to lipopolysaccharides that stems from Gram-negative enterobacteria, which are higher in MDD compared to controls [31], and which is associated with stress associated increased gut permeability and bacterial translocation in animal models [32, 33]. In addition, depression also altered the gut microbiota in a mouse model, in which chronic depression and anxiety-like behaviors were induced by olfactory bulbectomy [34], suggesting a feedback loop between depressive states and dysbiosis.

Furthermore, a similar type of relation between dysbiosis and psychopathogenesis is found in schizophrenia [35, 36]. For example, elevated levels of serological markers of bacterial translocation have been found to be highly correlated with systemic inflammatory markers in schizophrenia [37], and, cytokine levels in schizophrenia are correlated with the severity of symptomatology [38]. From a genetic point of view, several of the strongest associations identified between genetic risk and schizophrenia stems from genes that are linked to immunological function [57, 58]. This is particularly interesting in view of the genetic association between AN and schizophrenia [39].

3. How is the effects in the gut-brain axis mediated?

The mechanism behind the gut brain axis may be multifaceted involving neural signal transduction in nerveus vagus, neurotransmitters, immunological mechanisms, and mechanisms related to metabolism and energy utilization [40]. One of the strongest links from a mechanistic point of view, stems from research on serotonin and the microbiota. Enterochromaffin (EC) cells provides approximately 95% of the total body content of serotonin [41] of which the majority exists in plasma. Multiple levels of evidence links disturbances in the serotonergic system and several psychiatric disorder such as depression, anxiety, and borderline personality disorder. For example, the metabolism of tryptophan, a precursor of serotonin, is potentially regulated by the gut microbiota thereby enabling it to influence brain function [42]. Tryptophan is an essential amino acid derived from the diet [43], and tryptophan that is absorbed from the gut into the bloodstream passes the
blood-brain barrier to contribute to serotonin synthesis in situ [43]. The availability of tryptophan is strongly affected by the gut microbiota, and several studies have indicated that bacteria such as streptococcus, Escherichia, enterococcus species and *Bifidobacterium infantis*, and especially indigenous spore-forming bacteria may modulate serotonin levels by increasing plasma tryptophan [44]. An example of this is studies in germ free mice that have found that they exhibit an increased plasma tryptophan concentration [14, 15], which after post weaning colonization can be normalized [14]. The serotonergic neurotransmission may thereby be influenced by the availability of tryptophan for serotonin production [45]. There are studies have found that a depletion of tryptophan influences mood, anxiety and borderline personality traits, for example, in AN and bulimia nervosa [46–49].

There are also other evidences that link the gut microbiota with psychiatric conditions such as MDD. For example, a recent publication by Seng et al. [50] provides three additional levels of evidences: (a) that germ free mice lacks gut microbiota and display depression like features in forced swimming test compared to conventionally raised healthy control mice; (b) that the gut microbiota composition of MDD patients differ from that of healthy controls; and (c) and that transplantation of MDD microbiota to germ free mice led to the development of depression like behaviors. In addition, Seng et al. found that mice that were harboring the microbiota from MDD patients primarily exhibited disturbances of microbiome genes and host metabolism which thereby suggests that the depression-like behavior was mediated through the host metabolism [50].

Another neurotransmitter that is produced by the microbiota and that may influence host behavior is gamma aminobutyric acid (GABA) which is the main inhibitory neurotransmitter in the CNS. GABA produced by the probiotic *Lactobacillus rhamnosus* was administered to mice and led to an alteration in the expression of GABA receptors in different CNS regions, associated with reduced anxiety and depression-like behaviors [51].

Another mechanism for interaction between the microbiome and the CNS is at the level of the blood-brain barrier (BBB). The vascular BBB is comprised of specialized brain endothelial cells acts as a regulatory interface between brain and blood that prevent the unrestricted transfer of molecules into the CNS. Disruption of the tight junctions of the BBB can expose the CNS, and has also been linked to CNS disorders [52]. A dysbiotic microbiome could possibly interact with the BBB in several ways: bacterial factors and immune-active molecules released from peripheral sites influenced by the microbiome can cross the BBB, alter BBB integrity or change BBB transport [53]. In germ-free mice, it has been shown that the BBB has increased permeability compared to pathogen-free mice with a normal gut flora. The increased permeability was associated with reduced expression of the tight junction proteins. Exposure of germ-free adult mice to a normal gut microbiota decreased BBB permeability and up-regulated the expression of tight junction proteins [54]. Metabolic products such as short-chain fatty acids (SCFAs) are produced through the fermentation of dietary fibers by the gut microbiota [55] and can cross the BBB to affect brain function. A low production of SCFAs could lead to increased BBB permeability and SCFAs has been shown to be able to improve a dysfunctional BBB in germ-free mice [54]. Another example is that antibiotics are able to modify barrier integrity and alter behavior in mice [56] and alterations to the microbiome composition in mice in favor of, for example, probiotic *bifidobacteria* spp. through food supplement with prebiotics showed impact on neuroinflammation and were accompanied with changes in the expression of tight junction proteins [57]. Furthermore, leptin, a key hormone for the control of appetite and weight gain, is normally restricted by the BBB but has been shown in mice with a deficit in leptin transport to the brain to enhance the sense of food reward [58].
4. Microbiota findings in AN studies

Dysbiosis has been proposed in AN and through the long periods of starvation associated with the core psychopathology of AN, a considerable adaptation in gut microbiota could occur in individuals with AN. A systematic review by Schwennsen et al. [59] found some evidence of dysbiosis in AN, such as the abundance of the gut microbiota in AN, which was described as either normal [60, 61], reduced [62] or altered in AN [63]. In addition, the diversity of the gut microbiota in AN was described as normal [61, 63], or reduced (alpha, i.e., within-sample diversity) [64] both in the acute stage and after weight restoration.

Common microbiota findings in the acute stages of AN were low levels of phylum Bacteroidetes [61, 64], while the phylum Firmicutes was increased in AN in three studies [61, 64, 65] however decreased in a fourth [63]. Furthermore, the genus Methanobrevibacter and specifically, the species M. smithii, has been found increased in AN patients in several studies [60, 61, 63, 65]. It is important to remember the presence or lack of a specific bacterial spp. identified by their 16rRNA gene is not the same as the presence or lack of certain metabolic functions or microbiota steady-state dynamic. The state of knowledge of the microbiota in AN is in its infancy and more studies are needed.

4.1 The microbiota and relation to clinical symptoms in AN

This systematic review [59] identified two studies describing an association between the microbiota and clinical symptoms in AN. In one study, ClpB protein concentrations were significantly correlated with several subscales on the Eating Disorder Inventory-2 (EDI-2) for patients with eating disorders and the Montgomery-Åsberg Depression Rating Scale (MADRS) total score and specifically the anhedonia score for AN patients (p < 0.05) [66]. In another study, an association between alpha diversity and depression and eating disorder psychopathology was found in AN [64]. Should further studies find further support for that the microbiota drives the symptoms of AN, this would strengthen targeting the microbiota as a primary level of treatment of AN.

5. How is the gut-brain axis involved in AN? Breakdown of organic material in the gut and its exposure in plasma

A potential mechanism through which the microbiota indirectly influences the pathophysiology and symptoms of AN is through the breakdown of organic material in the gut and the transfer of metabolites into the blood stream. One of the microbiota that has been described in AN is M. smithii, which is involved in the breakdown of polysaccharides from vegetable sources and the finding of this specific Archaeon could illustrate an adaptation to a typical diet rich in vegetables and fruits in persons with AN. In addition, methanogenic Archaea, such as M. smithii, have also been linked to constipation, a common complaint in patients with AN, which statins have been shown to alleviate by suppressing the growth of methanogens [65, 67–69]. The evidence of M. smithii in feces from constipated patients necessitate further investigation of whether this finding in AN patients is only related to constipation or also related to AN psychopathology as a potential biomarker.

The gut microbiota is involved in both weight gain and weight loss as well as with energy extraction from the diet in both humans and animals [70, 71]. Differences in the composition of the gut microbiota between obese and lean individuals have been consistently described, potentially illustrating differences in energy extraction
efficiency between obese and lean individuals [72, 73], and specific gut dysbiosis could predispose to the drive toward negative energy balance in AN. With regard to the effect of weight gain on the fecal microbiota, Firmicutes has been found increased after weight restoration in two studies in AN [61, 64].

6. AN comorbid disorder as evidence of microbiota influence

Intestinal dysbiosis has previously been associated with psychological function and mental health including depression and anxiety, both of which are commonly comorbid with AN [40]. AN patients often present with comorbid anxiety (75% lifetime prevalence of anxiety disorder) [74] and depression (more than 34% lifetime prevalence of depression) [75, 76]. These findings provide further support for a role of dysbiosis in the pathophysiology of AN.

7. A leaking gut in AN?

During starvation, some of the gut bacteria will have insufficient nutrient supply for survival. Slowly growing bacteria or bacteria able to feed on the mucus lining the gut wall will survive for a longer period of time [77]. The competition between bacteria with different growth capacities to survive and proliferate in the gut has probably taken place for millions of years. Thus, it is reasonable to expect that various mechanisms for survival and proliferation have emerged among gut bacteria including the capacity to release of substances inhibiting food intake of the host. Alterations in gut permeability has been linked to a number of intestinal diseases, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), but also to extraintestinal disease as depression, anxiety and autism specter disorders [78, 79]. Increased gut permeability may also facilitate signal transduction from the gut to the brain via the vagus nerve and blood [80], possibly in synergy with interaction with increased BBB permeability. In addition, in animal and human studies, the experience of stress is also linked to an increase in permeability of the intestinal barrier. This increase in permeability seems to be mediated through, among other factors, hypothalamic hormones, especially corticotropi-releasing hormone (CRH) [77]. Increased mucin degrading bacteria has been demonstrated in AN [81] indicating that decreased food intake induce overgrowth of bacteria able to feed on the mucus layer and thereby increase gut permeability.

An example of a possible biomarker species is the bacterium Akkermansia muciniphila which is abundant in humans and rodents and has been inversely correlates with body weight and is associated with metabolic syndromes and auto-immune diseases [82]. A. municiphilia is a symbiotic bacterium of the mucus layer, can utilize mucin as its sole carbon, nitrogen, and energy source and is able to produce certain SCFAs [83, 84]. In mice, it has been shown that the abundance of A. muciniphila decreased in obese and type 2 diabetic mice and that administration of the bacterium increased the intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion [82]. In a single AN patient case story, it has been shown that one treatment with a fecal matter transplant from a healthy donor led to weight gain and an increase in A. muciniphila and SCFAs blood levels [85]. A. municiphilia is an example of a complex interaction where the bacterium simultaneously degrade the mucin for energy, but also at the same time induces higher mucus production from the host. This could in turn improve protection of the gut wall from interaction with harmful molecules from other gut bacteria and leakage into the blood.

Furthermore, in an activity based mouse model of AN Jésus et al. demonstrated increased permeability in the colon, that is, “gut leakiness”, in anorexic mice,
however the authors also found that the gut leakiness was more related to malnutrition than exercise [86]. Although there may be conflicting studies [87], yet another study examining the role of exercise on gut permeability, found that exercise increases intestinal permeability measured with the lactulose and rhamnose differential urinary excretion test [88].

Another support for a leaking gut wall in AN comes from a study by Breton et al. [66], who found an increase in ClpB protein concentrations in plasma in eating disorder patients compared to plasma of controls, and furthermore, that ClpB protein concentrations correlated positively with alpha-Melanocyte Stimulating Hormone-(alpha-MSH)-reactive IgG for all patients with eating disorders. ClpB protein is produced by Enterobacteriaceae such as Escherichia coli and has been found as a conformational mimetic of alpha-MSH, which is thought to be involved in satiety and anxiety [89]. The study adds evidence to the potential role of ClpB protein produced by Enterobacteriaceae in the gut and its impact on the brain and psychopathology in eating disorders.

The potentially altered gut permeability in AN may underlie the low-grade inflammation and increased risk of autoimmune diseases found in eating disorders [90]. Moreover, starvation has a significant impact on the gut microbiota, and a diet based on animal products used for re-nutrition, may stimulate the growth of bacteria that trigger inflammation [91].

8. A model for the pathophysiology of AN

The initial reduction of food intake induces alterations in the gut microbiota. These alterations in gut microbiota induce increased gut permeability. Due to this
altered microbiota and increased gut and in addition, increased blood-brain barrier permeability, neurohormonal signals interfering with food intake are transferred to the brain, influencing brain functions, for example, cognition. This contributes in creating a vicious circle which subserves in maintaining the mechanisms associated with AN (Figure 1).

9. Conclusions

There are a lot of evidence linking dysbiosis and inflammatory and psychiatric disorders and although there are only a few studies that have examined the microbiota in AN, several of these point to a dysbiosis also in AN. The effects of this dysbiosis is mediated through the gut-brain axis, and leakage through the gut and potentially also the BBB, provide pathways for neurohormonal signals to induce and maintain psychiatric disorders such as AN. The evidence in AN will need confirmation and further clarification in larger, randomized and controlled studies. We propose a model for disease development and maintenance in AN where a dysbiosis is a key component. Future studies will need to clarify the pathophysiology of AN.

Acknowledgements

We are thankful to Psychiatric Center Ballerup and the Capitol Region of Denmark, for providing support for this study.

Conflict of interest

The authors declare no conflict of interest.

Author details

Magnus Sjögren1,2,*, Stein Frostad3 and Kenneth Klingenberg Barfod4

1 Mental Health Center Ballerup, Ballerup, Denmark
2 Institute for Clinical Medicine, University of Copenhagen, Denmark
3 Department of Mental Health Research, Division of Psychiatry, Haukeland University Hospital, Bergen, Norway
4 Department of Veterinary and Animal Sciences, Section of Experimental Animal Models, University of Copenhagen, Denmark

*Address all correspondence to: jan.magnus.sjoegren@regionh.dk

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Keshaviah A et al. Re-examining premature mortality in anorexia nervosa: A meta-analysis redux. Comprehensive Psychiatry. 2014;55(8):1773-1784

[2] Steinhausen HC. Outcome of eating disorders. Child and Adolescent Psychiatric Clinics of North America. 2009;18(1):225-242

[3] Lock J, Le Grange D. Treatment Manual for Anorexia Nervosa: A Family-Based Approach. 2nd ed. New York; London: Guilford; 2013

[4] Treasure J, Russell G. The case for early intervention in anorexia nervosa: Theoretical exploration of maintaining factors. The British Journal of Psychiatry. 2011;199(1):5-7

[5] Eating Disorders: Recognition and treatment. Clinical Guideline, National Guideline Alliance (UK). London: National Institute for Health and Care Excellence; 2017. https://www.nice.org.uk/guidance/NG69 [Accessed 1 Mar 2019]

[6] Cooper Z, Fairburn CG. The evolution of “enhanced” cognitive behavior therapy for eating disorders: Learning from treatment nonresponse. Cognitive and Behavioral Practice. 2011;18(3):394-402

[7] Frostad S et al. Implementation of enhanced cognitive behaviour therapy (CBT-E) for adults with anorexia nervosa in an outpatient eating-disorder unit at a public hospital. Journal of Eating Disorders. 2018;6:12

[8] Quigley EMM. Gut bacteria in health and disease. Gastroenterology & Hepatology. 2013;9(9):560-569

[9] Claesson MJ et al. Comparative analysis of pyrosequencing and a phylogenetic microarray for exploring microbial community structures in the human distal intestine. PLoS One. 2009;4(8):e6669

[10] Qin J et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59-65

[11] Sudo N et al. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. Journal of Immunology. 1997;159(4):1739-1745

[12] Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003;361(9356):512-519

[13] Sudo N et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. The Journal of Physiology. 2004;558(Pt 1):263-275

[14] Clarke G et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular Psychiatry. 2013;18(6):666-673

[15] Diaz Heijtz R et al. Normal gut microbiota modulates brain development and behavior. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(7):3047-3052

[16] Cryan JF, O’Mahony SM. The microbiome-gut-brain axis: From bowel to behavior. Neurogastroenterology and Motility. 2011;23(3):187-192

[17] Neufeld KA, Foster JA. Effects of gut microbiota on the brain: Implications for psychiatry. Journal of Psychiatry & Neuroscience. 2009;34(3):230-231
Anorexia and Bulimia Nervosa

[18] Kennedy PJ et al. Irritable bowel syndrome: A microbiome-gut-brain axis disorder? World Journal of Gastroenterology. 2014;20(39):14105-14125

[19] Sternbach H, State R. Antibiotics: Neuropsychiatric effects and psychotropic interactions. Harvard Review of Psychiatry. 1997;5(4):214-226

[20] Bercik P et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011;141(2):599-609, 609 e1-3

[21] Liu Z et al. High-fat diet induces hepatic insulin resistance and impairment of synaptic plasticity. PLoS One. 2015;10(5):e0128274

[22] Daniel H et al. High-fat diet alters gut microbiota physiology in mice. The ISME Journal. 2014;8(2):295-308

[23] Sharma S, Fernandes MF, Fulton S. Adaptations in brain reward circuitry underlie palatable food cravings and anxiety induced by high-fat diet withdrawal. International Journal of Obesity. 2013;37(9):1183-1191

[24] Magnusson KR et al. Relationships between diet-related changes in the gut microbiome and cognitive flexibility. Neuroscience. 2015;300:128-140

[25] Bruce-Keller AJ et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. Biological Psychiatry. 2015;77(7):607-615

[26] Davey KJ et al. Gender-dependent consequences of chronic olanzapine in the rat: Effects on body weight, inflammatory, metabolic and microbiota parameters. Psychopharmacology. 2012;221(1):155-169

[27] Ley RE et al. Microbial ecology: Human gut microbes associated with obesity. Nature. 2006;444(7122):1022-1023

[28] Davey KJ et al. Antipsychotics and the gut microbiome: Olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. Translational Psychiatry. 2013;3:e309

[29] Hansen AK et al. A review of applied aspects of dealing with gut microbiota impact on rodent models. ILAR Journal. 2015;56(2):250-264

[30] Neufeld KM et al. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterology and Motility. 2011;23(3):255-264, e119

[31] Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endocrinology Letters. 2008;29(1):117-124

[32] Bravo JA et al. Communication between gastrointestinal bacteria and the nervous system. Current Opinion in Pharmacology. 2012;12(6):667-672

[33] Ait-Belgnaoui A et al. Acute stress-induced hypersensitivity to colonic distension depends upon increase in paracellular permeability: Role of myosin light chain kinase. Pain. 2005;113(1-2):141-147

[34] Park AJ et al. Altered colonic function and microbiota profile in a mouse model of chronic depression. Neurogastroenterology and Motility. 2013;25(9):733-e575

[35] Dinan TG, Borre YE, Cryan JF. Genomics of schizophrenia: Time to consider the gut microbiome? Molecular Psychiatry. 2014;19(12):1252-1257
[36] Nemani K et al. Schizophrenia and the gut-brain axis. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2015;56:155-160

[37] Severance EG et al. Discordant patterns of bacterial translocation markers and implications for innate immune imbalances in schizophrenia. Schizophrenia Research. 2013;148(1-3):130-137

[38] Fan X, Goff DC, Henderson DC. Inflammation and schizophrenia. Expert Review of Neurotherapeutics. 2007;7(7):789-796

[39] Duncan L et al. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. The American Journal of Psychiatry. 2017;174(9):850-858

[40] Rogers GB et al. From gut dysbiosis to altered brain function and mental illness: Mechanisms and pathways. Molecular Psychiatry. 2016;21(6):738-748

[41] Erspamer V. Pharmacology of indole-alkylamines. Pharmacological Reviews. 1954;6(4):425-487

[42] O’Mahony SM et al. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research. 2015;277:32-48

[43] Ruddick JP et al. Tryptophan metabolism in the central nervous system: Medical implications. Expert Reviews in Molecular Medicine. 2006;8(20):1-27

[44] Yano JM et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015;161(2):264-276

[45] Ben-Ari Y. Neuropaediatric and neuroarchaeology: Understanding development to correct brain disorders. Acta Paediatrica. 2013;102(4):331-334

[46] Kaye WH et al. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. The International Journal of Eating Disorders. 2003;33(3):257-267. Discussion 268-70

[47] Kaye WH et al. Effects of acute tryptophan depletion on mood in bulimia nervosa. Biological Psychiatry. 2000;47(2):151-157

[48] Smith KA, Fairburn CG, Cowen PJ. Symptomatic relapse in bulimia nervosa following acute tryptophan depletion. Archives of General Psychiatry. 1999;56(2):171-176

[49] Weltzin TE et al. Acute tryptophan depletion and increased food intake and irritability in bulimia nervosa. The American Journal of Psychiatry. 1995;152(11):1668-1671

[50] Zheng P et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Molecular Psychiatry. 2016;21(6):786-796

[51] Bravo JA et al. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(38):16050-16055

[52] Najjar S et al. Neurovascular unit dysfunction and blood-brain barrier hyperpermeability contribute to schizophrenia neurobiology: A theoretical integration of clinical and experimental evidence. Front Psychiatry. 2017;8:83

[53] Logsdon AF et al. Gut reactions: How the blood-brain barrier connects the microbiome and the brain. Experimental Biology
Anorexia and Bulimia Nervosa

[55] Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. Physiological Reviews. 2001;81(3):1031-1064

[56] Leclercq S et al. Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. Nature Communications. 2017;8:15062

[57] de Cossio LF et al. Impact of prebiotics on metabolic and behavioral alterations in a mouse model of metabolic syndrome. Brain, Behavior, and Immunity. 2017;64:33-49

[58] Di Spiezo A et al. The LepR-mediated leptin transport across brain barriers controls food reward. Molecular Metabolism. 2018;8:13-22

[59] Schwensen HF et al. A systematic review of studies on the faecal microbiota in anorexia nervosa: Future research may need to include microbiota from the small intestine. Eating and Weight Disorders. 2018;23(4):399-418

[60] Million M et al. Correlation between body mass index and gut concentrations of Lactobacillus reuteri, Bifidobacterium animalis, Methanobrevisbacter smithii and Escherichia coli. International Journal of Obesity. 2013;37(11):1460-1466

[61] Mack I et al. Weight gain in anorexia nervosa does not ameliorate the faecal microbiota, branched chain fatty acid profiles, and gastrointestinal complaints. Scientific Reports. 2016;6:26752

[62] Morita C et al. Gut dysbiosis in patients with anorexia nervosa. PLoS One. 2015;10(12):e0145274

[63] Borgo F et al. Microbiota in anorexia nervosa: The triangle between bacterial species, metabolites and psychological tests. PLoS One. 2017;12(6):e0179739

[64] Kleiman SC et al. The intestinal microbiota in acute anorexia nervosa and during renourishment: Relationship to depression, anxiety, and eating disorder psychopathology. Psychosomatic Medicine. 2015;77(9):969-981

[65] Armougom F et al. Monitoring bacterial community of human gut microbiota reveals an increase in lactobacillus in obese patients and methanogens in anorexic patients. PLoS One. 2009;4(9):e7125

[66] Breton J et al. Elevated plasma concentrations of bacterial ClpB protein in patients with eating disorders. The International Journal of Eating Disorders. 2016;49(8):805-808

[67] Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proceedings of the National Academy of Sciences of the United States of America. 2006;103(26):10011-10016

[68] Gottlieb K et al. Review article: Inhibition of methanogenic archaea by statins as a targeted management strategy for constipation and related disorders. Alimentary Pharmacology & Therapeutics. 2016;43(2):197-212

[69] Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. Journal of Neurogastroenterology and Motility. 2014;20(1):31-40

[70] Flint HJ. Obesity and the gut microbiota. Journal of...
Clinical Gastroenterology. 2011;45(Suppl):S128-S132

[71] Cox LM, Blaser MJ. Pathways in microbe-induced obesity. Cell Metabolism. 2013;17(6):883-894

[72] Aguirre M et al. In vitro characterization of the impact of different substrates on metabolite production, energy extraction and composition of gut microbiota from lean and obese subjects. PLoS One. 2014;9(11):e113864

[73] Turnbaugh PJ et al. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480-484

[74] Godart NT et al. Anxiety disorders in anorexia nervosa and bulimia nervosa: Co-morbidity and chronology of appearance. European Psychiatry. 2000;15(1):38-45

[75] Fernandez-Aranda F et al. Symptom profile of major depressive disorder in women with eating disorders. The Australian and New Zealand Journal of Psychiatry. 2007;41(1):24-31

[76] Kask J, Ekselius L, Brandt L, Kollia N, Ekbom A, and Papadopoulos FC. Mortality in women with anorexia nervosa: The role of comorbid psychiatric disorders. Psychosomatic Medicine. 2016;78(8):910-919

[77] Herpertz-Dahlmann B, Seitz J, Baines J. Food matters: How the microbiome and gut-brain interaction might impact the development and course of anorexia nervosa. European Child & Adolescent Psychiatry. 2017;26(9):1031-1041

[78] Goyette P et al. Molecular pathogenesis of inflammatory bowel disease: Genotypes, phenotypes and personalized medicine. Annals of Medicine. 2007;39(3):177-199

[79] Spiller RC. Overlap between irritable bowel syndrome and inflammatory bowel disease. Digestive Diseases. 2009;27(Suppl 1):48-54

[80] Ntranos A, Casaccia P. The microbiome-gut-behavior axis: Crosstalk between the gut microbiome and oligodendrocytes modulates behavioral responses. Neurotherapeutics. 2018;15(1):31-35

[81] Mack I et al. Is the impact of starvation on the gut microbiota specific or unspecific to anorexia nervosa? A narrative review based on a systematic literature search. Current Neuropharmacology. 2018;16(8):1131-1149

[82] Everard A et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(22):9066-9071

[83] Derrien M et al. The Mucin degrader Akkermansia muciniphila is an abundant resident of the human intestinal tract. Applied and Environmental Microbiology. 2008;74(5):1646-1648

[84] Zhai Q et al. A next generation probiotic, Akkermansia muciniphila. Critical Reviews in Food Science and Nutrition. 2018:1-10. https://doi.org/10.1080/10408398.2018.1517725

[85] de Clercq NC, Frissen MN, Davids M, Groen AK, and Nieuwdorp M. Weight gain after fecal microbiota transplantation in a patient with recurrent underweight following clinical recovery from anorexia nervosa. Psychotherapy and Psychosomatics. 2019;88:58-60

[86] Jesus P et al. Alteration of intestinal barrier function during activity-based
anorexia in mice. Clinical Nutrition. 2014;33(6):1046-1053

[87] Monteleone P et al. Intestinal permeability is decreased in anorexia nervosa. Molecular Psychiatry. 2004;9(1):76-80

[88] Pals KL et al. Effect of running intensity on intestinal permeability. Journal of Applied Physiology (Bethesda, MD: 1985). 1997;82(2):571-576

[89] Kishi T, Elmquist JK. Body weight is regulated by the brain: A link between feeding and emotion. Molecular Psychiatry. 2005;10(2):132-146

[90] Raevuori A et al. The increased risk for autoimmune diseases in patients with eating disorders. PLoS One. 2014;9(8):e104845

[91] Devkota S et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in IL10−/− mice. Nature. 2012;487(7405):104-108