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Published in:
Current opinion in psychiatry

DOI:
[10.1097/YCO.0000000000000350](https://doi.org/10.1097/YCO.0000000000000350)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Koopman, M., El Aidy, S., & MIDtrauma Consortium (2017). Depressed gut? The microbiota-diet-inflammation triologue in depression. *Current opinion in psychiatry*, 30(5), 369-377.
<https://doi.org/10.1097/YCO.0000000000000350>

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Depressed gut? The microbiota-diet-inflammation triad in depression

Margreet Koopman^a, MIDtrauma consortium^{b,c,d}, and Sahar El Aidy^a

Purpose of review

According to the WHO reports, around 350 million people worldwide suffer from depression. Despite its high prevalence, the complex interaction of multiple mechanisms underlying depression still needs to be elucidated.

Recent findings

Over the course of the last few years, several neurobiological alterations have been linked to the development and maintenance of depression. One basic process that seems to link many of these findings is inflammation. Chronic inflammation has been associated with both biological factors such as excessive neurotransmitter concentrations as well as psychological processes such as adult stress reactivity and a history of childhood trauma. As a balanced microbial community, modulated by diet, is a key regulator of the host physiology, it seems likely that gut microbiota plays a role in depression.

Summary

The review summarizes the existent literature on this emerging research field and provides a comprehensive overview of the multifaceted links between the microbiota, diet, and depression. Several pathways linking early life trauma, pharmacological treatment effects, and nutrition to the microbiome in depression are described aiming to foster the psychotherapeutic treatment of depressed patients by interventions targeting the microbiota.

Keywords

antidepressants, food for mood, inflammation, leaky gut, major depressive disorders, microbiome

INTRODUCTION

Major depressive disorder (MDD) is the leading psychiatric disorder worldwide, resulting in significant economic and emotional strain on society. Yet treatment outcomes remain suboptimal: one in two patients do not adequately respond to treatment, 40% of responders relapse, and many nonresponders deteriorate in spite of treatment [1]. Thus, a detailed understanding of the complex interactions between the neurobiology and environmental factors driving the development of this disorder is needed to enhance treatment outcomes.

Recently, the gut microbiome has been suggested to play a role in determining who would develop pathological levels of depression. This review aims at summarizing the existent literature on this emerging research field and providing a comprehensive overview of the multifaceted links between the gut microbiota and MDD.

MICROBIOTA, DIET, AND INFLAMMATION; CRITICAL MEDIATORS IN DEPRESSION

The neurobiology of depression is multifactorial and multiinteractional with genetic, transmitter-related, and neuronal alterations. Genetic alterations on different levels of analysis have recently been detailed [2]. Neural alterations associated with MDD

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Curr Opin Psychiatry 2017, 30:369–377

DOI:10.1097/YCO.0000000000000350

KEY POINTS

- 'Leaky gut hypothesis' of MDD links inflammation and gut microbiota to depression.
- Gut microbiota impacts depression development via serotonergic systems.
- Interventions targeting the microbiota are promising tools to modulate depression.

have been described regarding both brain structure [3,4] and brain function [5] and recently neural subtypes of depression have been identified [6].

However, there is also ample evidence that psychological precursors such as childhood trauma are closely linked to the occurrence of depression [7], indicating a strong neuroplastic interaction of neurobiological with childhood maltreatment [8[¶]] and childhood trauma is associated with a higher likelihood of earlier depression onset and the development of treatment-resistant depression. The neurobiological long-term effects of childhood trauma are complex and have been described ranging from genetics to brain function (for a comprehensive review see [9]).

In the past, it has been proven difficult to integrate the knowledge across different levels of analysis as suggested by the Research Domain Criteria approach (<https://www.nimh.nih.gov/research-priorities/rdoc>). What is missing are theoretical models integrating these different predictors by providing causal links and explanatory mechanisms.

Despite the disconfirming reports, one phenomenon explaining alterations in MDD across several levels of analysis, however, seems to be persistent inflammation (for a review see [10[¶]]). The failure to resolve an inflammatory process in due time has been linked to both biological factors such as excessive neurotransmitter concentrations because of genetic and epigenetic changes [11] as well as psychological processes such as adult stress reactivity and a history of childhood trauma [12]. Inflammatory processes seem to even be translationally predictive of the effect of antidepressant medication [13].

Recently, independent lines of research have converged on identifying one potential key player in the inflammatory process and the levels of available neurotransmitters: the gut microbiota, that is, the combination of gut bacteria resident in the human intestine. Rodent experiments recently indicated that depression is correlated with altered composition of the microbiota (summarized in Table 1 and recently reviewed in [20,21]). Moreover,

rodent models indicate that the microbiota reacts with altered immunoregulatory responses to both acute and chronic psychological stress [22], thus potentially linking psychological factors to neurobiological agents and even neural alterations. It has been argued that the effect of antidepressant medication can at least in part be linked to its antimicrobial activity [23] and, that psychotherapeutic treatment effects can reverse the associated changes in inflammation [24].

EARLY LIFE EVENTS, ALTERED MICROBIOTA COMPOSITION, AND RISK OF DEVELOPING MAJOR DEPRESSIVE DISORDER

It is now well established that the early gut colonizers mediate the effects of early life events on adult behaviour. Early life establishment of the immune system is heavily influenced by the colonization with diverse commensals, which offers a plethora of antigens that are crucial for appropriate maturation of the immune system [25,26]. Notably, there is also increasing evidence that there is mutual interaction between the microbiota and the effects of early life on brain function and development. Using maternal separation as an early life stressor in rats lead to both anxiety and depressive-like behaviours as well as significant changes in the composition of the intestinal microbiota [27,28]. However, this seems to be a two-way street: we have recently shown that alterations in the expression of serotonin transporters in the brain result in an imbalance in the microbial population in rats, particularly when combined with exposure to early life stress [29].

Early microbial colonization is also linked to activation of the hypothalamic–pituitary–adrenal (HPA) axis, which in turn impacts the enteric nervous system that innervates the gut [30,31]. The beneficial effects of the early colonizing microbiota in developing the immune and nervous systems, extracting nutrients from food and keeping harmful microbes at bay [32], support the concept of a critical window of development during the early life. This notion coincides with the microbiota deficiency hypothesis, which postulates that colonization with a 'healthy' microbiota during the vulnerable developmental period exerts effects that may decrease susceptibility to diseases, whereas its absence may have adverse effects [33]. Thus early life trauma might either impact the process of microbial colonization itself, or might have differential effects based on how the microbiota influenced the HPA axis in early life development. That childhood trauma is indeed linked to significant elevations of

Table 1. Overview of animal experiments and human trials that showed an association between major depressive disorder and altered gut microbiota composition

(Pre)clinical trial	Model	Type of intervention	Behavioural testing	Assay/microbiota composition analysis	Results	Reference
MDD patients/ animal trial	Male GF Kunming mice Male SPF Kunming mice	MDD patients' faecal microbiota transplantation Microbiota composition	Open field test, Y maze, tail suspension test, forced swimming test	16S ribosomal RNA sequence-based approach	Overrepresented in MDD patients Actinomycineae Coriobacterineae Lactobacillaceae Streptococcaceae Clostridiales Incertae Sedis XI Eubacteriaceae Lachnospiraceae Anaerostipes <i>Blautia</i> <i>Dorea</i> Insertae Sedis Ruminococcaceae Clostridium IV Erysipelotrichaceae Incertae Sedis Kunming Mice Overrepresented in control study participants Bacteroidaceae Rikenellaceae <i>Alistipes</i> Lachnospiraceae Coprococcus <i>Clostridium</i> XIVa Incertae Sedis <i>Roseburia</i> Faecalibacterium Acidaminococcaceae Phascolarctobacterium Veillonellaceae Megamonas Sutterellaceae	[14]
MDD patients/ animal trial	Male Sprague-Dawley rats	MDD patients' faecal microbiota transplantation	Sucrose preference, open field, elevated plus mace, forced swimming test	Illumina Miseq platform	Overrepresented in control study participants Prevotellaceae Prevotella Dialister Overrepresented in MDD patients Thermoanaerobacteriaceae Eggerthella Holdemania Gelria Turicibacter Paraprevotella Anaerofilum	[15]
Animal trial	Male C57BL/6JmSlc mice	Exposure to subchronic and mild social defeat stress	None	Metabolic analysis of cecal content via capillary electrophoresis time-of-flight	Overrepresented in stressed animals Rikenellaceae Lachnospiraceae Alobaculum Underrepresented in stressed animals <i>Allabaculum</i> <i>Mucispirillum</i>	[16]
Animal trial	Male C57BL/6J mice WT	Exposure to chronic restraint stress	Rotarod, elevated plus maze, marble burying test, open field test, sucrose preference test, novelty suppressed feeding, forced swimming test	16S rRNA analysis	Underrepresented in chronic restraint stress <i>Allobaculum</i> Bifidobacterium Turicibacter <i>Clostridium</i> Overrepresented in chronic restraint stress Lachnospiraceae	[17]

Table 1 (Continued)

(Pre)clinical trial	Model	Type of intervention	Behavioural testing	Assay/microbiota composition analysis	Results	Reference
Animal trial	Male BALB/cAnNTac mice	High sucrose/high-fat diet	Sucrose preference test, burrowing test, triple test, forced swimming test, Morris water maze	High throughput sequencing	Effect of high-fat diet higher abundances of Ruminococcaceae Lachnospiraceae Lower abundances of Bacteroidetes	[18]
Human trial	Depressed patients and normal controls	Serum concentration measurements of IgA and IgM against LPS	None	ELISA to measure levels of IgA, IgM produced in response to preselected microbiota	Increased IgM response against selected microbiota: <i>Hafnia Alvei</i> <i>Pseudomonas Aeruginosa Morganella Morganii</i> <i>Pseudomonas Putida</i> Increased IgA response against selected microbiota: <i>Hafnia Alvei</i> <i>Pseudomonas Aeruginosa Morganella Morganii Klebsiella Pneumoniae</i>	[19]

GF, germ free; LPS, lipopolysaccharides; MDD, major depressive disorder; SPF, specific pathogen free.

proinflammatory HPA transmitters has recently been reconfirmed in a large meta-analysis [34].

GUT MICROBIOTA AND INFLAMMATORY MECHANISMS OF MAJOR DEPRESSIVE DISORDER

We are only beginning to understand the widespread interaction of the intestinal microbiota with the immune and the neuroendocrine systems. The emerging data suggest several pathways via which the microbiota can exert an influence on the whole psychoneuroimmunology network [35]. Intestinal microbiota may coordinate the neuroendocrine-immune dialogue via several mediators including epithelial cells, (mucosal) immune cells as well as peripheral neurons [36,37]. Below, we will discuss how each pathway suggests a link between the microbiota and risk of developing MDD (Fig. 1).

The leaky gut hypothesis

A growing body of evidence highlights the ‘leaky gut hypothesis’ as a possible mechanism mediating inflammation in MDD [38].

In healthy study participants, the majority of the gut microbiota is kept at bay so that they have no direct contact with the host’s intestinal cells. However, in states of disease and microbial imbalance (known as dysbiosis), potentially pathogenic bacteria are capable of invading host tissues and can manipulate them into activating the local immune

FIGURE 1. An overview of potential links between the gut microbiota, diet inflammation, and the development of depression. HPA, hypothalamic–pituitary–adrenal.

cells and associated parts of the enteric nervous system [39]. The 'leaky gut' hypothesis of MDD is based on this abnormal immune response, which in turn is mediated by the so-called toll-like receptor-4 (TLR-4). Supporting this hypothesis, a recent study demonstrated that both TLR-4 signalling was upregulated and a marker for bacterial DNA was found in newly diagnosed patients with MDD [24]. After cognitive behavioural therapy, the same cohort of 50 patients showed significant reduction of proinflammatory markers, which was associated with clinical improvement during psychotherapy. Interestingly, TLR-4 has recently also emerged as a potential mechanism by which the brain monitors peripheral immune responses, thus linking changes in the microbiota to the prefrontal cortex [40]. The dual role of TLR-4 signalling pathway after stress exposure was further supported by a study using stress exposure in mice. In contrast to wild-type mice exposed to stress, mice deficient in TLR-4 and mice treated with antibiotics to change their microbiota did not show elevated levels of inflammation markers [41]. These results suggest a protective role of antibiotic treatment in MDD via the impact antibiotics have on the microbiota.

In addition, the production of proinflammatory cytokines has been linked both to specific compositions of the microbiota and the development of depression in mice and men:

For example, the gut microbiota *Lactobacillus* spp. have been implicated in elevation of proinflammatory cytokines in depressed patients via its ability to activate components of the innate immune system [17] (Table 1). Collectively, reports from animal and human studies suggest that the modulation of cross-talk between stress, gut microbiota, and neuroinflammation could alter brain function, and affect depressive and anxiety-like behaviours.

In depression specifically, the secretion of proinflammatory cytokines has been linked to the experience of childhood trauma, independent of current stress levels [42]. This link is further supported by reports indicating that chronic stress increases the gut permeability hence leading to a 'leaky gut' in rats and that these adverse effects can be reversed by probiotics [43]. These findings were further supported by data from human studies, which indirectly suggest increased bacterial translocation (i.e. 'leaky gut') in stress-related psychiatric disorders such as depression [44]. In fact, increased concentrations of inflammatory cytokines are known to circumvent the mechanisms of action of conventional antidepressants, further suggesting that inhibition of the inflammatory cytokines would potentially be an additional pathway to reducing

depressive symptoms. This assumption was confirmed by the results of a placebo-controlled, randomized clinical trial showing that an inflammatory cytokine antagonist reduces depression symptoms in a subset of patients with high baseline inflammatory biomarkers [45].

The gut microbiome influences the immune system via the production of neurotransmitters

One way by which the microbiota communicate with the immune system is via molecules called neurotransmitters: immune cells travelling through the blood might be attracted by these neurotransmitters [46]. Moreover, the proinflammatory cytokines released through this microbiota-induced immune response can in turn have a direct influence on the secretion of neurotransmitters such as norepinephrine [47], or indirectly via influencing the enzyme that converts levo dopa to dopamine and norepinephrine [48] and the enzyme that metabolizes monoamines; serotonin, norepinephrine, and dopamine. Particularly, reduction of the levels of the latter enzyme has been associated with MDD (referred to as 'the monoamine theory') [49].

These data are intriguing in light of the known link between the changes in the levels of several neurotransmitters, such as serotonin, gamma amino butyric acid (GABA), dopamine, norepinephrine, and corticotropin-releasing hormone, inflammation, and MDD. In mice, oral administration of the probiotic *Lactobacillus rhamnosus* JB-1 resulted both in alterations in the composition of the gut microbiome and in reductions in depression-related behaviours. These changes were likely mediated by alterations in the GABA receptors in specific brain regions and a subsequent attenuation of the HPA axis response [50]. This is in line with research indicating that mice with compromised microbiota composition show a hyperactivity of the HPA axis [51], that GABA receptors in the frontal cortex play a key role in MDD, and that antidepressants can upregulate these receptors [52].

Particularly, effects on the serotonergic system are of importance because of its strong link to MDD [53]. Apart from its function in neurotransmission, serotonin also has an anti-inflammatory effect [54]. Reduction in the levels of serotonin may thus not only lead to aberrant neurotransmission and its subsequent effect on mood directly, but may also have indirect effects via increased inflammatory reactions. [55,56]. Moreover, a direct link between the gut microbiota, stimulation of specified cells for the production of serotonin in the gut epithelium,

and the overall production of serotonin has been recently shown [57²²]. Notably, serotonin-related immune reactions elicited by environmental biological stressors are functionally and anatomically different from immune reactions elicited by anxiety-inducing stimuli or uncontrollable stressors [58]. Activation of the immune system via the bacterium *Mycobacterium vaccae* resulted in increased serotonin metabolism within the ventromedial prefrontal cortex and altered stress-related emotional behaviour. These data might indicate a protective role of the gut microbiota via activation of serotonergic neurons. Similarly, treatment with serotonergic antidepressant drugs prevents the onset of depressive symptoms in patients with comorbid irritable bowel syndrome [59,60], who in turn are characterized by a significantly altered gut microbiome composition [61].

In conjunction, these findings suggest that serotonergic systems could be a plausible route by which the gut microbiota coordinates the immune–neuroendocrine communication and impacts MDD development. Whether the results to date reflect a causative or reactionary response is yet to be elucidated.

EFFECT OF ANTIDEPRESSANT DRUG TREATMENT ON THE GUT MICROBIOTA?

Specific changes in the microbiota composition during major depressive episodes have been identified [62]: MDD patients showed increases in Bacteroidetes, Proteobacteria, and Actinobacteria as well as a specific decrease in Firmicutes (see Table 1).

One way to study the causal direction of these findings is through transplantation of faecal material collected from patients with MDD in experimental animals. It was recently demonstrated that rats showed more depression-like behaviour as well as an increase in MDD-associated inflammatory markers after such a faecal transplantation [15²³] (Table 1). This strongly suggests that alterations of the gut microbiota associated with depression could actually be a cause, rather than a consequence of the disorder.

It has been argued that the effect of several antidepressant medication including selective serotonin reuptake inhibitors can at least in part be linked to its antimicrobial effects [23]. Although selective serotonin reuptake inhibitors are directed against Gram-positive bacteria such as *Staphylococcus spp.* and *Enterococcus spp.* [63], tricyclic antidepressants can prevent the growth of intestinal pathogens, such as *Escherichia coli*, *Yersinia*

enterocolitica [64]. Through their antimicrobial activity, antidepressants might restore a healthy composition of the gut microbiota and hence reestablish homeostasis at the gut–brain interphase.

Deciphering the actual contribution of the antimicrobial effects of antidepressants for MDD treatment as well as determining the long-term consequences of these effects to gut microbiota composition and their implications to clinical outcomes is crucial for the development of microbiota-derived therapeutic alternatives.

FOOD FOR MOOD

Given the emerging role of the microbiota in depression and the fact that what we eat can significantly change the composition of our microbiota, it is no surprise that nutrition and depression are also linked. A recent study indicated that alterations in the microbiota composition elicited by nutrition are associated with altered neurotransmitter concentrations, which in turn are linked to cognitive impairments [65]. A diet characterized by nutrient-poor, energy-dense processed foods links depression to obesity [66,67] via several pathways: nutrition can influence hormonal, neurotransmitter, and signalling pathways, which in turn modulate several brain processes impacting both appetite and mood [68]. In addition, the experience of childhood trauma has been linked to obesity and elevated levels of inflammation markers are linked to childhood trauma via the obesity of the patient [69]. This suggests that restoring the gut microbiota composition via nutritional interventions could be an indirect strategic tool to treat MDD. For example, inadequate intake of ω -3 polyunsaturated fatty acids has been associated with impaired mental health [70] and several studies have shown that their supplementation can improve depressive symptoms and effectively reverse the effects of early life stress in rats [71]. A diet low in unsaturated fatty acids for pregnant mice resulted in depressive-like behaviour and altered composition of the gut microbiota in their offspring [72]. Significant differences in the composition of the microbiota were observed during adolescence and adulthood, in a similar trend as has been reported in obese versus lean study participants [73]. These results indicate that the maternal diet and nutrition during early life developmental period influences behaviour and gut microbiota composition later in life.

Tryptophan, a precursor of serotonin, is altered in MDD patients [15²⁴,74] and this alteration might also be mediated by the microbiota: in germfree mice, circulating tryptophan levels were higher in the absence of the gut microbiota [75–77].

Consumption of more traditional healthy Mediterranean style diet rich in fruits, vegetables, legumes, olive oil, fish, and whole grains is associated with reduced depression [78]. Interestingly, these components are typical prebiotics (nutrition for gut bacteria), which represent another channel to alter the gut microbiota. Probiotic supplements, also showed an anxiolytic effect in healthy human study participants (for a comprehensive review see [79], likely mediated by an altered HPA axis response to stress [80].

CONCLUSION

Although the bidirectionality of the multiple interactions between the microbiota, the immune system and the brain has not been fully understood yet, the current data seem to indicate that alterations in the microbiota of depressed patients might not just be a consequence of the disorder, but might exert causal influence on the symptom development. Several neurotransmitters such as serotonin have been identified by which the microbiota communicate with the immune system and which might also act as neurotransmitters in the brain. Given the ample evidence for altered serotonin levels in depressed patients, it might be worth considering how the microbiota can be influenced to act salutogenetically. Surprisingly, at least parts of the treatment effect of psychotropic medication might actually be mediated via altering the microbiota and thus the secretion of these neurotransmitters. In addition, alterations in nutrition might open a window of opportunity that hitherto has not been fully appreciated. Finally, if one extrapolates from emerging research on rodents, the transplantation of microbiota from healthy study participants might evolve as a suitable intervention in the future.

In conjunction, the pathways linking the gut microbiota to neural activation in the brain might be a lot shorter than most clinicians appreciate. Hopefully, the psychotherapeutic treatment of depressed patients can be fostered by interventions targeting the microbiota.

Acknowledgements

None.

Financial support and sponsorship

J.K.D. and S.E.A. are supported by Rosalind Franklin Fellowships, cofunded by the European Union and University of Groningen.

Conflicts of interest

There are no conflicts of interest.

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