Microbiota-Gut-Brain Axis: Is Gut Microbiota Correlated with Major Depressive Disorder (MDD)?

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INTRODUCTION

The gut microbiota is crucial during the development of the nervous system and has influence, through the microbiota-gut-brain axis, on several psychological disorders such as anxiety, major depressive disorder (MDD), schizophrenia and autism spectrum disorder (ASD). MDD is a debilitating disease that is characterized by one or more discrete depressive episodes of at least two weeks' duration involving clear-cut changes in affect, cognition, and vegetative symptoms. Some of the biological dysregulations associated to depression affect the inflammatory and oxidative stress, metabolism, Hypothalamic-Pituitary-Adrenal (HPA) axis, and neurotransmitter and neuropeptide production; which are all processes modified by the gut microbiota. In addition to that, psychobiotics are probiotics that confer a health benefit on patients with psychiatric problems when administered in adequate doses. Psychobiotics are being studied as a potential alternative for treatments that present adverse symptoms such as tryptophan supplementation, or as supplements for treatments with tricyclic antidepressants and monoamine oxidase inhibitors.

Methodology: For the realization of the present review, a systematic data research was carried out mainly in *Pubmed* database provided by the National Center for Biotechnology Information, ScienceDirect and GoogleScholar.

Objectives**:** 1) The main objective is to answer the question: Is gut microbiota correlated with Major Depressive Disorder (MDD)?; 2) Gather information from trustworthy sources in order to write up a complete report about the crosstalk between the gut and the brain through the Microbiota-Gut-Brain; 3) Gain knowledge about the effect that gut microbiota upon Major Depression Disorder, as well as its mechanisms of action; 4) Review which probiotics can be used to ameliorate depressive-like behaviors and its future clinical perspectives.

RESULTS

MAJOR DEPRESSIVE DISORDER (MDD)

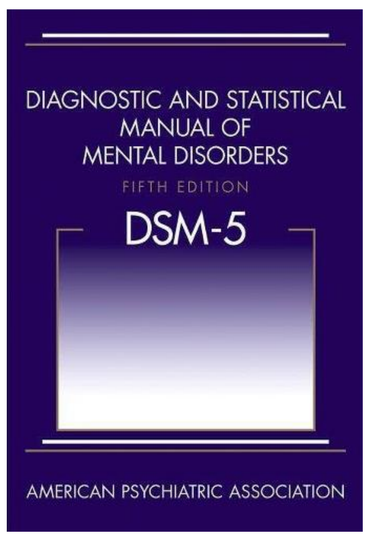


Figure 1. DSM-5 book cover

HOW IS MDD DIAGNOSED?

- Presence of 2 or more symptoms during 2 weeks
- Symptoms cause distress and impairment
- Episode is not caused by drugs or medical condition
- Episode is not explained by other mental disorders
- Individual has never had a maniac episode

GUT MICROBIOTA AND MICROBIOTA-GUT-BRAIN AXIS

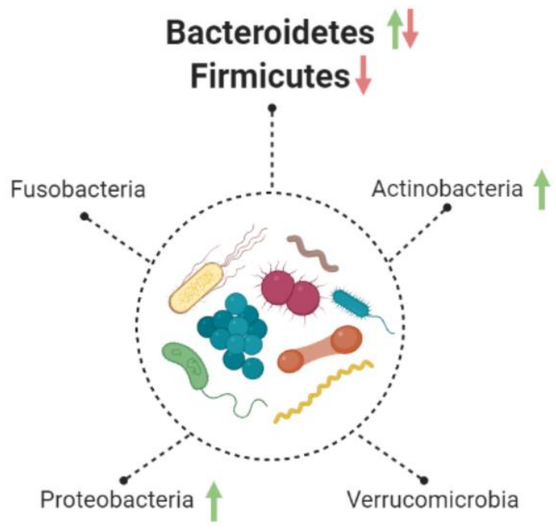
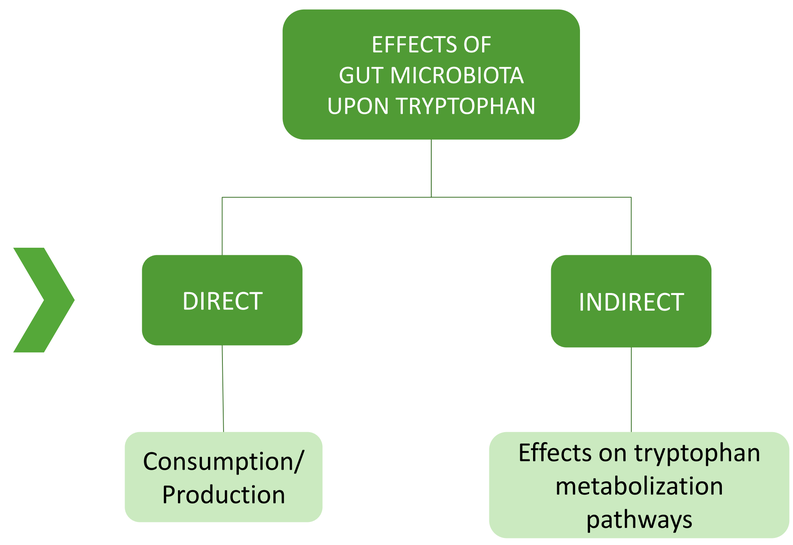


Figure 2. Most abundant bacterial phyla present in human gut and its alterations in depression



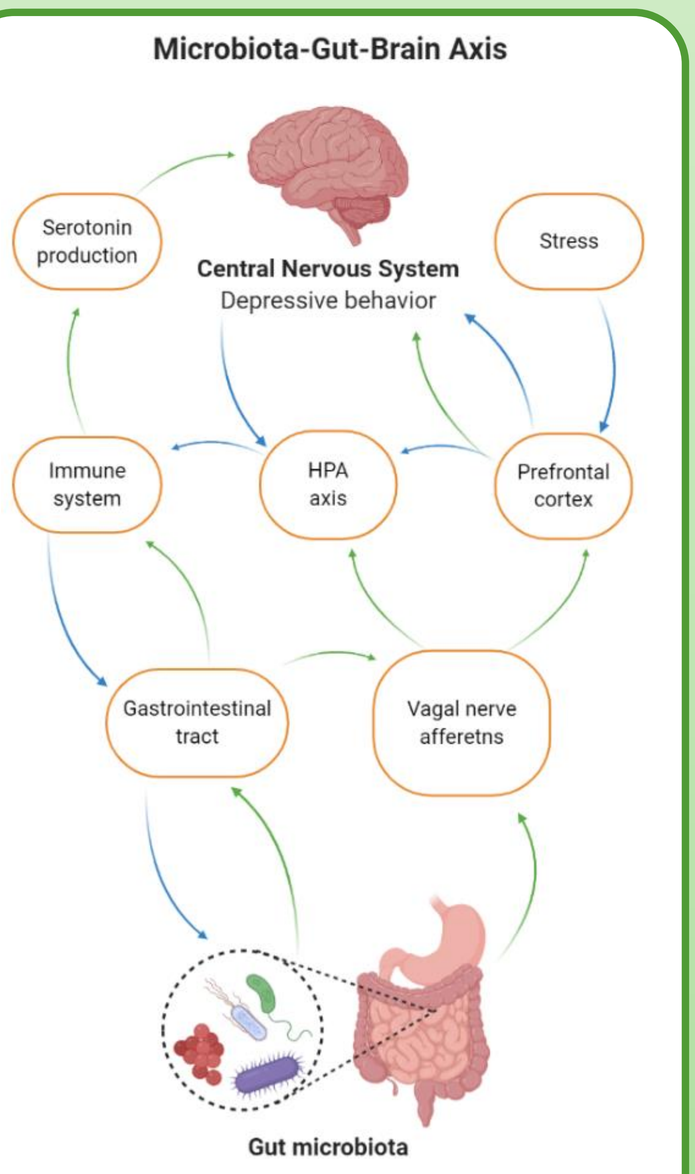


Figure 3. Microbiota-Gut-Brain axis and its brain to gut (blue arrows) and gut to brain (green arrows) communication pathways. Adapted from Winter et al., 2018.

Data from animal studies provides evidences that gut microbiota may impact the neurobiological features of depression, such as: low-grade immune activation, HPA axis activity, altered tryptophan metabolism, amongst others. Experimental data suggests a complex bidirectional interaction between the gastrointestinal tract and the central nervous system (CNS), commonly named "Gut-Brain axis". Given that it has also been seen a role of the gut microbiota in this interaction, the term MGB axis was coined.

GUT MICROBIOTA IN SEROTONIN PRODUCTION

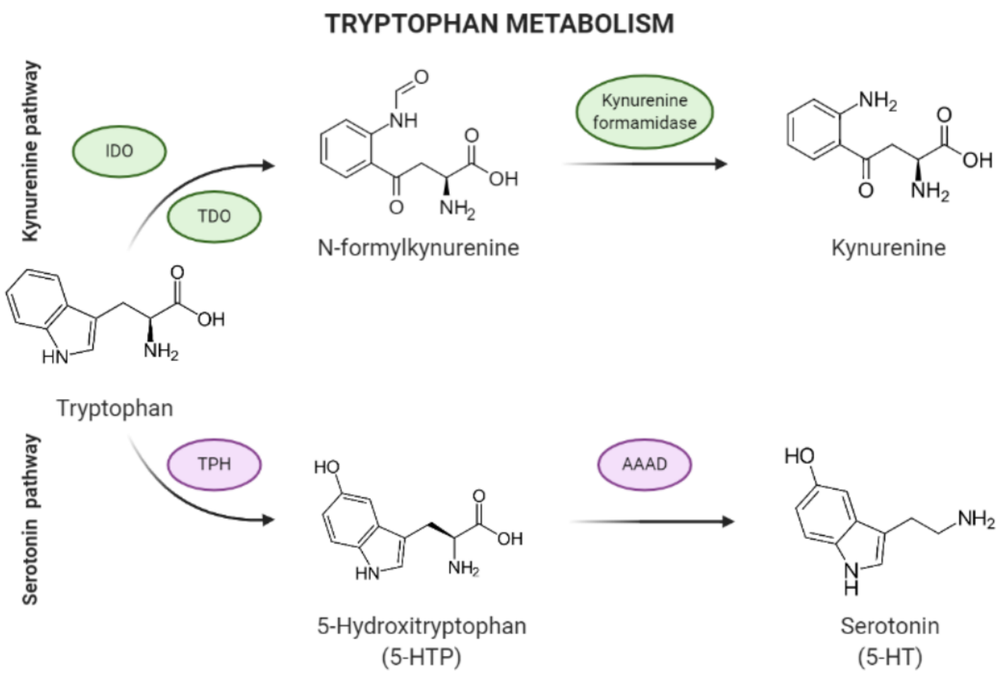


Figure 4. Tryptophan metabolization pathways. indoleamine-2,3-dioxygenase (IDO), tryptophan-2,3-dioxygenase (TDO), tryptophan hydroxylase (TPH), aromatic amino acid decarboxylase (AAAD)

Tryptophan is an essential amino acid that must be supplied in the diet, since eukaryotes do not generate the enzyme needed for its synthesis. Then it can be accumulated and used in two different body regions:

1) It can be absorbed in the gut, put into circulation and cross the blood brain barrier and participates in serotonin synthesis in the CNS.
2) It is used to produce serotonin in the enterochromaffin cells of the gastrointestinal tract.

However, tryptophan metabolism is separated into two pathways: the kynurenine and serotonin pathways (KYN and 5-HT respectively).

Kelly et al, carried out a study in which patients suffering from depression showed increased plasma levels of IL-1, IL-6 and TNFα, as well as a higher KYN/TRP ratio compared to control individuals. Hence, a correlation can be established between the increased level of these cytokines and the induction of the enzyme indoleamine-2,3-dioxygenase (IDO), which consequently has an impact in the KYN/TRP ratio, and ultimately, in serotonin production.

Bifidobacterium infantis AS A PSYCHOBIOTIC

Within the world of probiotics there is a subgroup denoted as psychobiotics, which confer a health benefit to patients with psychiatric problems when administered in adequate doses.

Desbonnet et al., 2008 assessed the potential antidepressant properties of *Bifidobacterium infantis* 35624 in rats, and the overall results of the study are the following:

1) *B. infantis* administration caused an IFN-γ production suppression, which was accompanied by an increase in plasma tryptophan.
2) A decrease in the kynurenine:tryptophan ratio suggests a reduced activity of IDO, which is likely to be due to the reduced levels of pro-inflammatory cytokines.
3) Increase in the kynurenic acid:kynurenine ratio, which is known as the neuroprotective ratio, due to an up-regulation of kynurenic acid production upon probiotic treatment

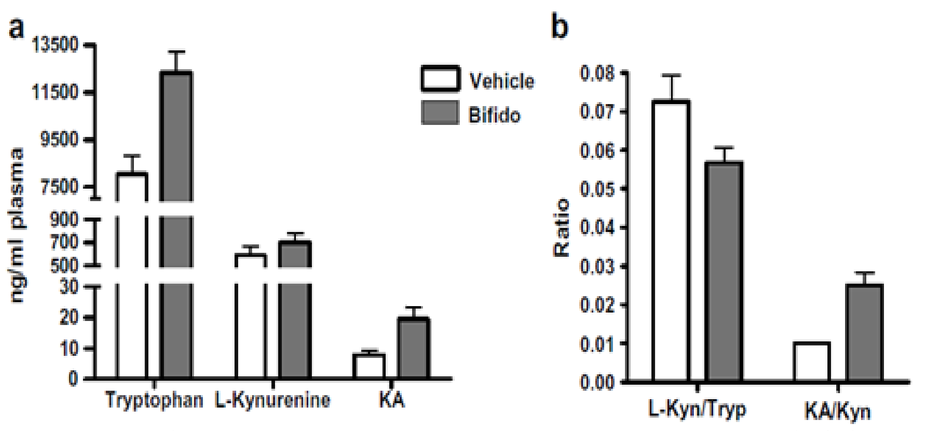


Figure 5. Graph a) shows tryptophan, L-kynurenine and kynurenic acid levels in plasma (ng/ml). Graph b) shows L-kynurenine/tryptophan and kynurenic acid/kynurenine rations. Grey bars refer to rats supplemented with *Bifidobacterium infantis*. Extracted from Desbonnet et al., 2008

CONCLUSIONS

- Depression is a multifactorial disorder that has several possible causes, which are related and influenced by each other.
- Studies on the crosstalk between gut microbiota and CNS focusing on depression, bring up interesting results and promising research lines that might help us to elucidate which are the causes, mechanisms and consequences of depression.
- Depression can potentially be caused by a dysregulation in the tryptophan metabolization as a consequence of a gut microbiota dysbiosis, which ultimately causes a decrease in serotonin production. Therefore, there is a correlation between gut microbiota and MDD.
- Psychobiotics can be used as a treatment or treatment supplementation in order to ameliorate depressive-like symptoms and promote serotonin production.

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