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TRYPTOPHAN METABOLISM IN MAJOR DEPRESSIVE DISORDER: A LINK BETWEEN THE BRAIN AND THE GUT MICROBIOTA

Júlia Cabré Torrents - Bachelor's Degree final project - Microbiology - 2022/2023

INTRODUCTION

"All disease begins in the gut" Hippocrates, 400 b.C.

The connection between the brain and the gut has been the subject of research for decades, but in recent years, the involvement of the gut microbiota in gut-brain communication has become the focus of scientific interest.

The gut microbiota has a key role in regulating intestinal and extraintestinal homeostasis. Furthermore, recent studies have demonstrated that it can also affect brain function, and thereby contribute to the pathogenesis of several psychiatric disorders, such as major depressive disorder (MDD), schizophrenia, or bipolar disorder.

RESULTS

A) MAJOR DEPRESSIVE DISORDER

MDD is a mood disorder that causes a persistent feeling of sadness and loss of interest. The precise mechanism by which it develops remains unclear, but for what is currently known it is related to four biological aspects, as shown in Figure 1. The microbiota-gut-brain axis (MGBA) may play a role in its development, as numerous studies have reported gut microbiota dysbiosis in depressed patients. The most commonly described results are represented in Figure 2, but the alterations are not consistent across all studies.

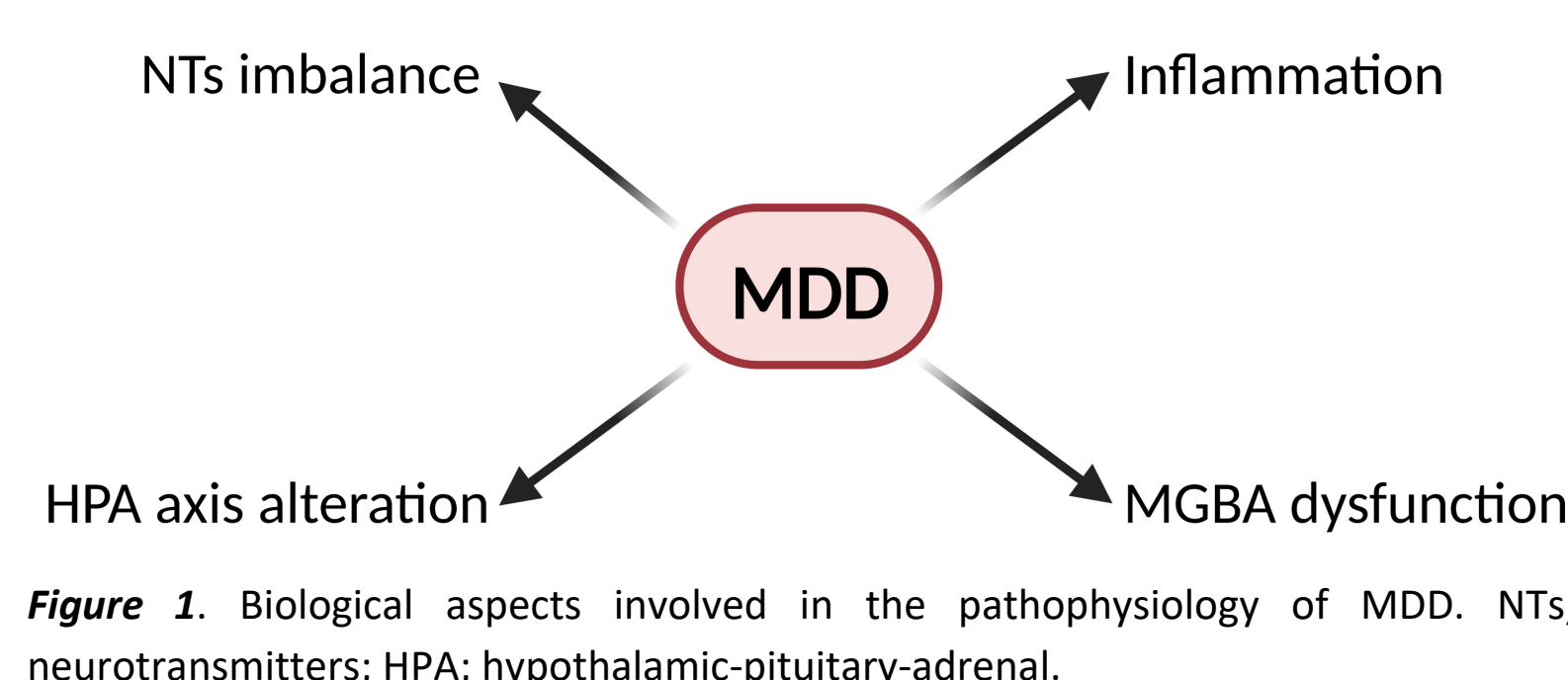


Figure 1. Biological aspects involved in the pathophysiology of MDD. NTs, neurotransmitters; HPA, hypothalamic-pituitary-adrenal.

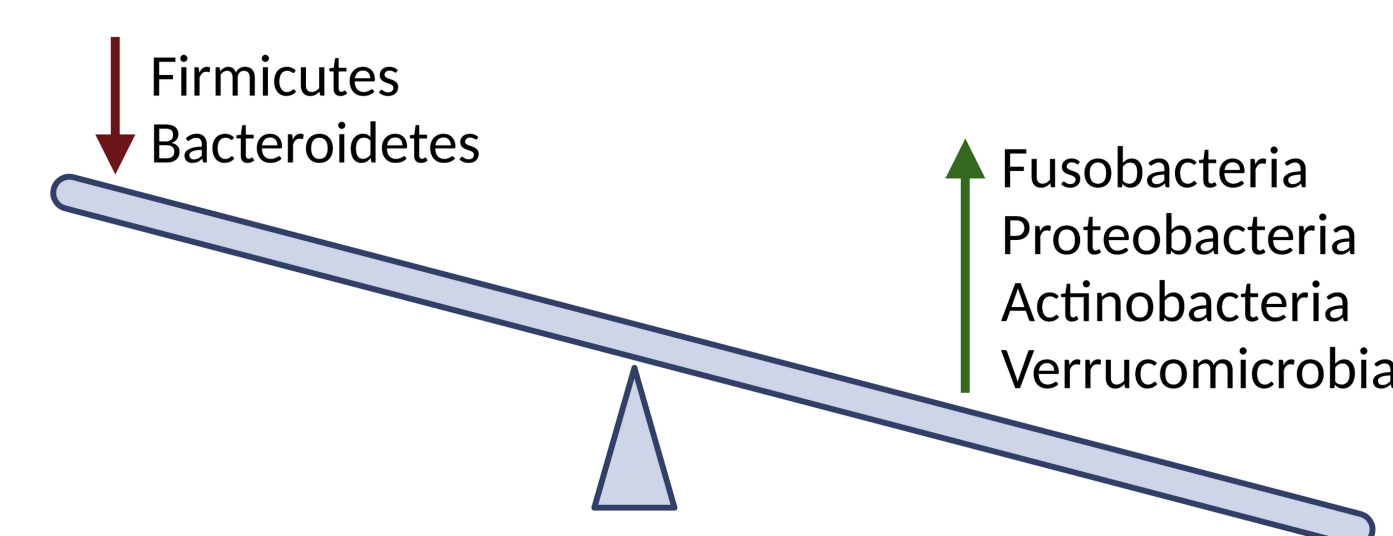


Figure 2. The most common alterations in the gut microbiota described in MDD patients

C) TRYPTOPHAN METABOLISM

Tryptophan (TRP) is an essential amino acid obtained exclusively from the diet. Once in the gastrointestinal tract, it can follow three pathways:

- Kynurenine (KYN) pathway (90%). TRP is metabolized into KYN, which is further converted into kynurenic acid (KYNA, neuroprotective) or quinolinic acid (QUIN, neurotoxic).
- Serotonin pathway. TRP can be converted into serotonin in the brain, but mainly (90%) it is synthesized in the gut by enterochromaffin cells.
- Microbial pathway. Includes the production of indole and its derivatives, tryptamine, and serotonin by the gut microbiota.

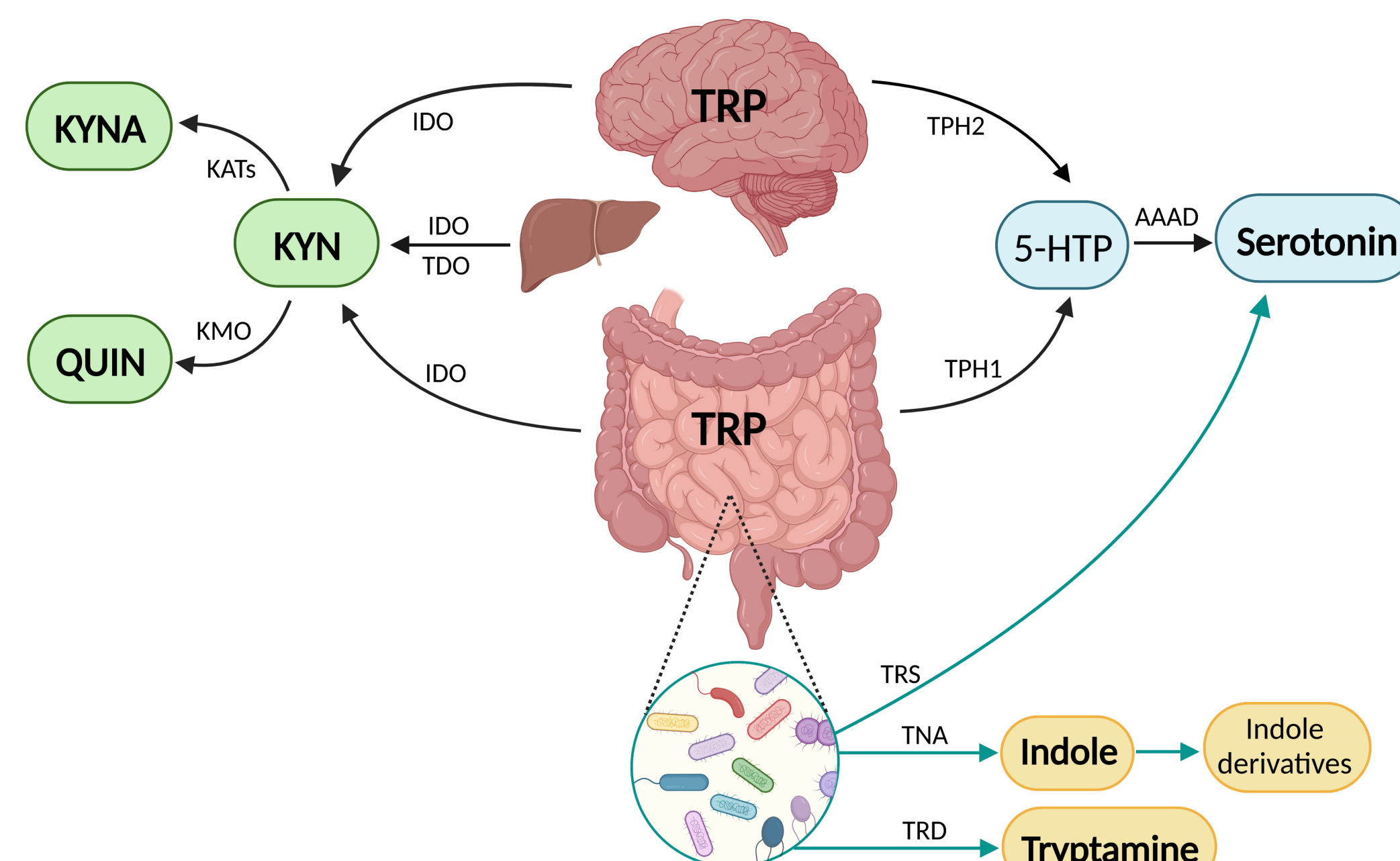
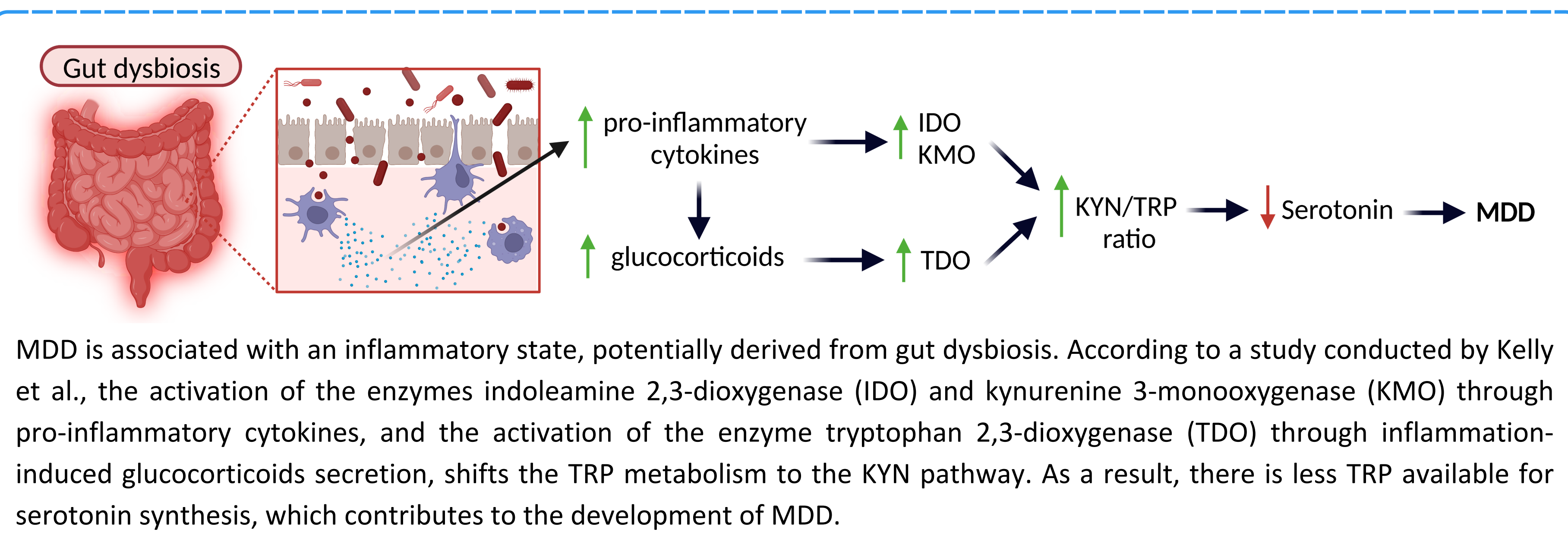


Figure 4. Tryptophan metabolism and the MGBA. The host (black arrows) and the microbial (blue arrows) pathways are shown. KATs, kynurenine aminotransferases; TPH, tryptophan hydroxylase; 5-HTP, 5-hydroxytryptophan; AAAD, aromatic amino acid decarboxylase; TRS, tryptophan synthetase; TNA, tryptophanase; TRD, tryptophan decarboxylase. Adapted from reference 2.



MDD is associated with an inflammatory state, potentially derived from gut dysbiosis. According to a study conducted by Kelly et al., the activation of the enzymes indoleamine 2,3-dioxygenase (IDO) and kynurenine 3-monooxygenase (KMO) through pro-inflammatory cytokines, and the activation of the enzyme tryptophan 2,3-dioxygenase (TDO) through inflammation-induced glucocorticoids secretion, shifts the TRP metabolism to the KYN pathway. As a result, there is less TRP available for serotonin synthesis, which contributes to the development of MDD.

METHODOLOGY

For the realization of the present review, a systematic data research was carried out in *Pubmed* and *Google Scholar* databases.

OBJECTIVES

The main purpose of this review is to examine the current state of knowledge on the role of the gut microbiota in the development of MDD.

B) MICROBIOTA-GUT-BRAIN AXIS

The term MGBA refers to bidirectional communication between gut bacteria and the brain. It includes signalling via four pathways.

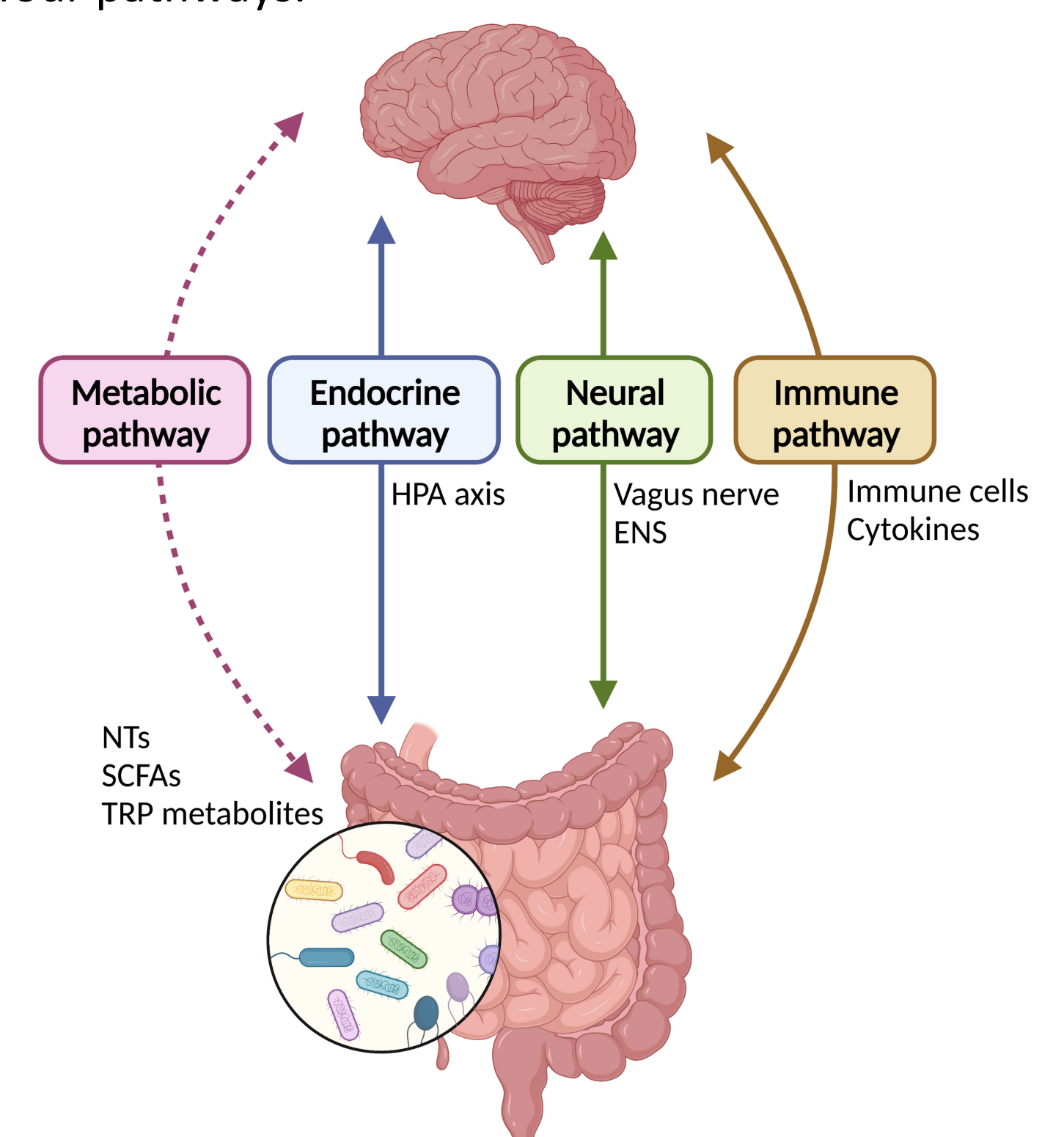


Figure 3. A schematic representation of the MGBA. SCFAs, short-chain fatty acids; TRP, tryptophan; ENS, enteric nervous system. The dotted line indicates a recently proposed pathway. Adapted from reference 1.

D) THERAPEUTIC PERSPECTIVES

The modulation of the gut microbiota with psychobiotics has become a subject of study for MDD treatment. Psychobiotics include probiotics and prebiotics that influence bacteria-brain relationships.

Prebiotic studies are scarce, but regarding probiotics some preclinical studies have yielded promising results. Desbonnet et al. evaluated the potential antidepressant properties of *Bifidobacterium infantis* in rats. The results were the following:

- Reduced production of pro-inflammatory cytokines, which led to a decrease in the KYN/TRP ratio.
- Increased KYNA/KYN ratio as a result of increased KYNA production.

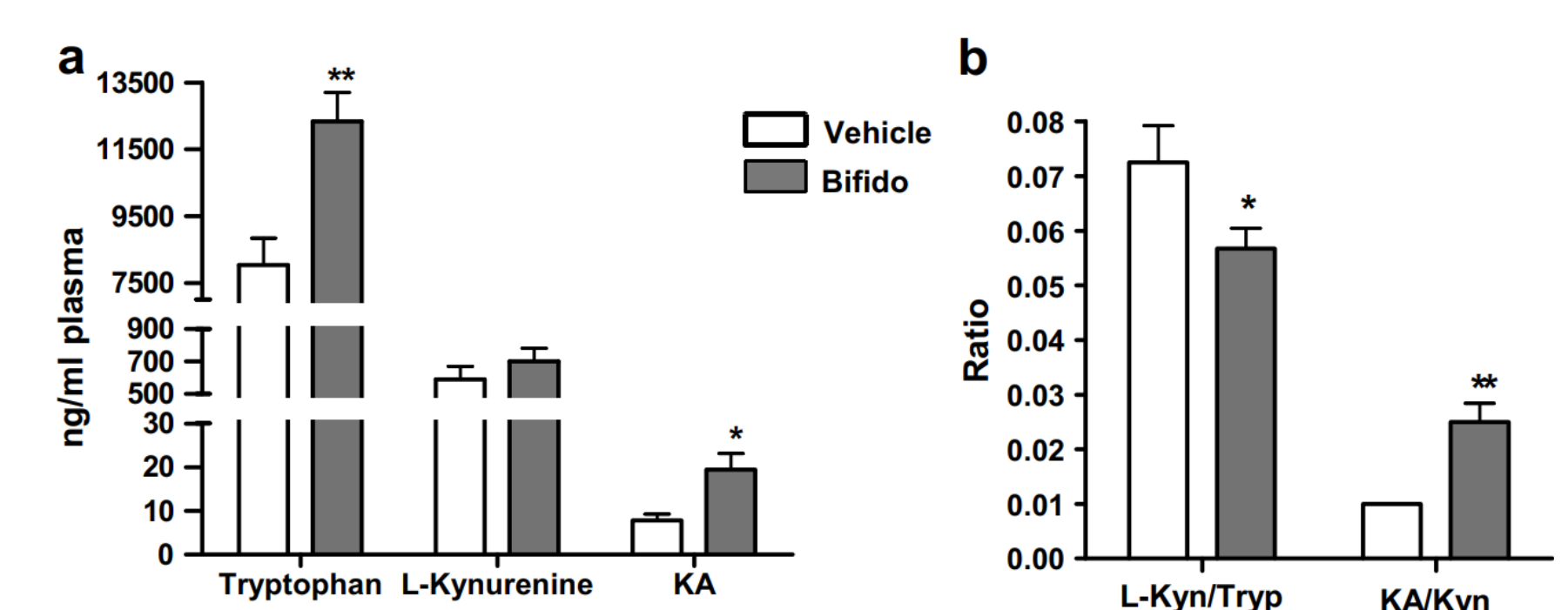


Figure 5. Plasma concentrations of tryptophan, L-kynurenine, and kynurenic acid (a), and L-kynurenine/tryptophan and kynurenic acid/kynurenine ratios (b). Grey bars refer to rats supplemented with *Bifidobacterium infantis*. Extracted from reference 4.

CONCLUSIONS

- ✓ MDD is a multifactorial disease, and recent research has demonstrated that the gut microbiota plays a role in its development.
- ✓ Several studies have reported gut microbiota dysbiosis in MDD patients, but no common pattern has been identified. It also remains unknown whether those changes are the cause or the result of the disease.
- ✓ MDD can potentially be caused by an alteration in the host's tryptophan metabolism as a consequence of the inflammation derived from gut microbiota dysbiosis, which eventually results in a decrease in serotonin production.
- ✓ Psychobiotic treatment could be a promising strategy to treat MDD. However, more clinical evidence is necessary to confirm such effects in humans, and the current possibility of using them is limited by numerous unknowns.

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