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Exploring the Relationship between Gut Microbiome and Depression

Shail Adrian Jagmag, Naveen Tripathi, Mainak Pratim Jha, and Sukant Khurana*

Department of Biological Sciences, Indian Institute of Science Education and Research –Kolkata, Mohanpur - 741246, Nadia, West Bengal, India

***Corresponding Author:** Sukant Khurana, Department of Biological Sciences,Indian Institute of Science Education and Research - Kolkata, Mohanpur - 741246, Nadia, West Bengal, India; E-mail: sukantkhurana@gmail.com, sukant.khurana@iiserkol.ac.in

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Abstract

In recent years the connection between gut microbiome and central nervous system depression has received major attention. In this review, we explore the status of literature on changes in microbiome that are associated with depression. We highlight animal studies that point to the possibility of curing depression, using changes in the gut microbiome. We then catalogue and speculate on the possible mechanisms behind the action of gut microbiota in influencing depression. Finally, we focus on the knowledge of demographic variability that would come in handy, if gut microbiome changes become a widespread method of curing depression.

Keywords: Central nervous system; Depression; Gut microbiome; Microfauna; Microflora; Excreta; Probiotic therapy; Antibiotic; Nude mice; Microbial replacement; Inflammation; Interleukins.

Introduction

Depression has a negative impact on sizable population of humans across the globe and it leaves visible scars in families and economies. Recent knowledge that depression can have links with diet, the fact that microorganisms can influence it and microbial replacement can help in its cure; have resulted in palpable excitement in the neuroscience community. Figure 1 illustrates the currently held view [1-6] on gut microbiota and depression connection.

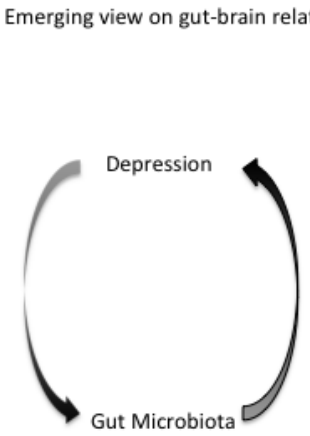

Figure 1: Emerging view on relation between depression and gut microbiota.

Gut Microbiota Changes Associated with Depression

Several microorganisms that are found in normal human beings as commensal and symbiotic gut residents show altered levels of expression in depressed subjects. We briefly provide few examples in Figure 2 of common eubacteria to illustrate the changes. Gut residents are not just confined to eubacteria. Various fungal genera, such as *Alterneria*, *Cladosporium*, *Aspergillus*, *Candida*, *Debaryomyces*, *Meyerozyma*, *Pichia*, *Saccharomyces*, *Fusarium*, *Rhodutorula*, *Cryptococcus*, *Cystofilobasidium* are found frequently in human gut and so are several protozoan genera, such as *Entamoeba*, *Giardia* and *Pentatrichomonas*and even several helminths. The bacterial genera that have been best characterized for depression changes are *Roseburia*, *Phascolarcto bacterium Megamonas*, *Lachnospiraceaincertae*, *Clostridium*, *Blautia*, *Ruminococcus*, *Dialister*, *Oscillibacter*, *Parasutterella*, *Parabacteroides*, *Alistipes*, *Prevotella Faecali bacterium* and *Bacteroides* [7-10].

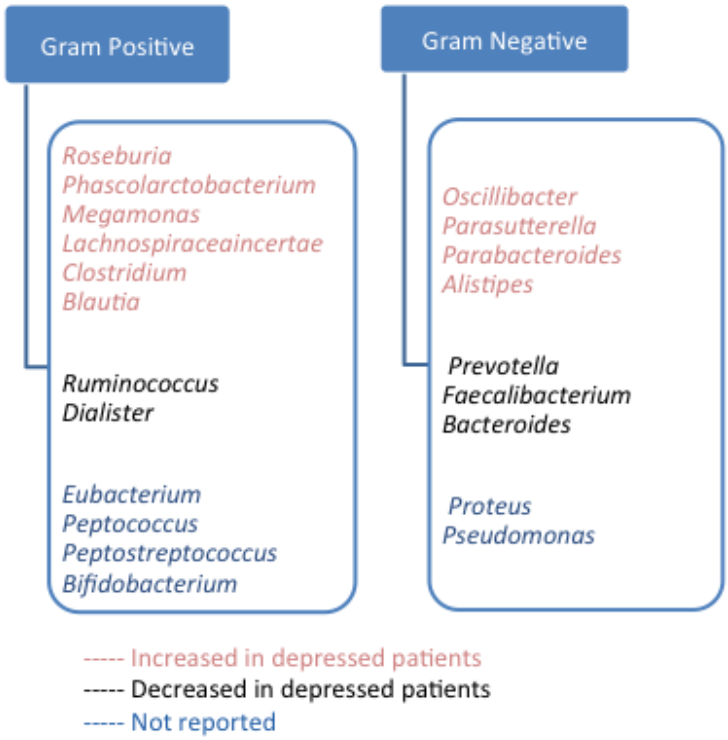

Figure 2: Few examples of common gut eubacteria genera. The pink are bacteria that are found to be higher in number in depressed patients and black to be lower in depressed patients than balanced controls. Bacteria in blue are the ones that we currently do not know, if they change in depressed patients.

Changes in Rodents in Response to Probiotics

Lab animals, especially rodents have been extensively used to study the possibility of altering gut microbiota to induce behavioral changes. Both the induction of anxiety and depression associated behaviours and also amelioration of such responses has been observed on treatment of rodents with different probiotics, establishing the potential of probiotic therapy at least in animal models. Figure 3 shows few examples of such probiotic therapy. *Bifidobacteriuminfantis* can reverse elevated HPA axis response and depression in rodents [11, 12]. *Bifidobacteriuminfantis* has been referred to as "psychobiotic" due to its antidepressant effects [11, 12].*Lactobacillus farciminis* has been reported to suppress stress induced changes in HPA axis activity, endotoxaemia and neuroinflammation [13]. *Lactobacillus rhamnosus*can decrease both anxiety and depression-like symptoms in mice [14]. *Lactobacillus helveticus* along with *Bifidobacterium longum* combination has been shown to decrease anxiety [15]. *Campylobacter jejuni*on the other hand has been shown to induce anxiety like behavior, without inducing immune responses [16].

The clinical work in humans is a few years behind rodent work and so far few studies have started to show potential of probiotic therapy [17-20]but there is a long way to go before probiotics become the staple as antidepressants.

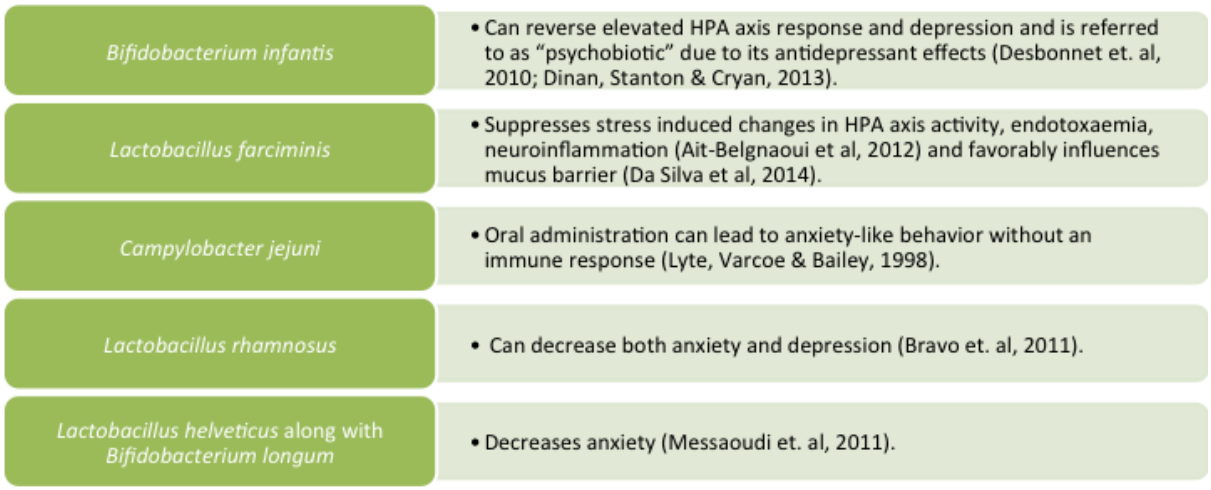

Figure 3: Changes observed in rodents in response to probiotics.

Possible Mechanisms of Action of Probiotics

The role of microorganisms in mood regulation, anxiety and depression is just beginning to be established. Our understanding of mechanisms is perfunctory at the best but already few very exciting roles of gut microbiota are emerging. In figure 4, we present possible mechanisms of action of gut microbiota. The mechanisms range from synthesis, absorption or modulation of rates of synthesis of various growth factors, neurotransmitters and neuromodulators.

While mechanistic steps and signalling in microbial activity regulating the uptake, modulation of synthesis and activity of various factors that can influence depression symptoms is largely unknown but a large body of literature has accumulated on the various influences. We provide few representative examples. GABA receptor mRNA expression in mice is modulated by ingestion of *L. Rhamnosus*[14]. Tryptophan metabolism alteration is associated with western diet-induced anxiolytic effects in mice [21]. Human and mouse derived gut microbiota have been shown to promote 5-HT and Tph 1 production [22]. Antibiotic induced depletion of gut microbiota in mice has been associated with overall decrease in serum tryptophan level and decrease in BDNF in hippocampus [23]. Choline bioavailability from diet can be modulated by *Anaerococcushydrogenalis*, *Clostridium asparagiforme*, *Clostridium hathewayi*, *Clostridium sporogenes*, *Edwardsiellatarda*, *Escherichia fergusonii* isolated from human samples [24].

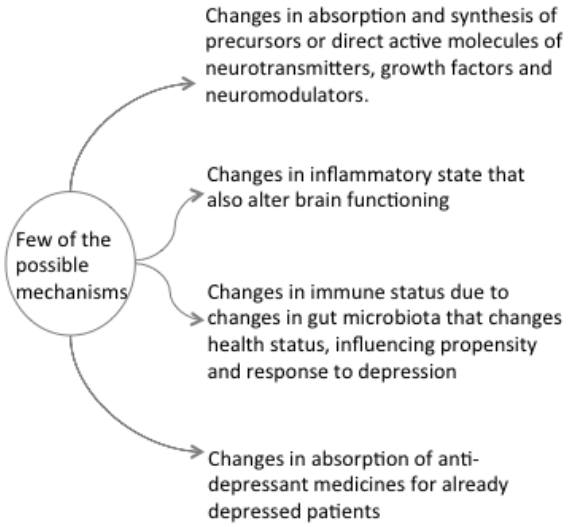

Figure 4: Possible mechanisms of depression status alteration by changes in gut microbiota.

Interestingly even direct synthesis of neurotransmitters and neuromodulators has been reported. *Clostridium sporogenes* has been reported to produce the neurotransmitter tryptamine by decarboxylating tryptophan [25]. An *Oscillibacter* strain producing valeric acid as its main metabolic end product, which is a homolog of the neurotransmitter GABA has also been observed [26]. There are several serotonin producing bacterial strains, such as *Lactococcuslactis* subsp. *Cremoris, L. lactis*subsp. lactis, *Lactobacillus plantarum, Streptococcus thermophiles* [27].

E. coli contains micromolar concentrations of L-DOPA and nanomolar of serotonin, dopamine, and norepinephrine during the late growth phase[28]. A strain of *L. plantarum* has been reported to produce acetylcholine [29]. GABA producing strains of *L. brevis, B. adolescentis, B. dentium, B. infantis*have been reported[30].

In addition microorganisms directly influence immune responses. Histamine-producing bacterial strains have also been reported from Lactococcuslactis subsp. Cremoris, L. lactis subsp. lactis, Lactobacillus plantarum, Streptococcus thermophilus M. morganii, K. pneumoniae, H. alvei[31].

Summary

Use of probiotics and change in dietary habits to cure depression and anxiety is a very fascinating possibility. With increasing number of studies finding more potential microbes that can alter depression status and mechanisms through which they act, the goal of finding alternative anti-depression therapies has started appearing much more tractable in the last few years.

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SK conceived the idea and guided the writing. SAJ, NT, and MPJ conducted literature survey and helped with writing. SK was funded by intramural grants from IISER-K. SAJ was funded by CSIR PhD. fellowship.

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