VIEWPOINT

Gut Microbes and Depression: Still Waiting for Godot

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The brain-gut-microbiota axis is viewed by some as a major paradigm shift in mental illness with the potential for the development of entirely novel therapies, while others have expressed scepticism regarding the approach(Dinan and Cryan 2017). What is now abundantly clear is the fact that the gut microbiota is a major source of metabolic activity and that such activity influencing all organs, including the brain. The routes of communication between the gut microbes and the brain have been partially established in rodents but far less is known about such routes in humans(Dinan, Cryan et al. 2018). The vagus nerve, short chain fatty acids, tryptophan and cytokines have all been implicated in gut to brain connectivity. That altered gut microbes (dysbiosis) might negatively impact gut to brain signalling in disorders such as depression is becoming an important field of study. The study from Jiang and colleagues (Jiang, Ling et al. 2015), winner of the 2019 BBI Impact Award, is a landmark in this respect, as almost all of the studies prior to this were preclinical in nature.

The slightly earlier study of Naseribafrouei et al recruited thirty-seven patients with depression and eighteen non-depressed controls(Naseribafrouei, Hestad et al. 2014) . They found no differences in diversity between the two groups, though they did report several correlations between depression and the faecal microbiota. The study is limited by a small sample size, especially of healthy controls. The Jiang et al paper had been widely cited because it was the first publication to report an altered gut microbiota in depressed patients. The dysbiosis detected was an increase in microbial diversity in acutely depressed patients, which was an unexpected finding. The general assumption has been that increased diversity is a positive health benefit, a fact which is especially true in the elderly where a lack of diversity is associated with frailty. Interestingly, such changes were not seen in those depressives who had responded to treatment. This may be explained by the fact that psychotropic medications have a major impact on the gut microbiota(Cussotto, Strain et al. 2018). In a subsequent similar study, the APC group also found a dysbiosis in depression, but in contrast the alteration consisted of decreased microbial diversity (Kelly, Borre et al. 2016). When rodents underwent a faecal microbiota transplant (FMT) from depressed patients they developed an anhedonic behavioural phenotype with increases in acute phase proteins and altered tryptophan metabolism. Given the increasing use in gastroenterology of FMT as a treatment for *C. difficile* infection, the studies lend support for the view that psychiatric profiling of the faecal donor is essential.

Insert Fig 1 here

The largest study to date comes from the Jeroen Raes group who studied the relationship between gut bacteria and quality of life and depression(Valles-Colomer, Falony et al. 2019). They combined faecal microbiome data with general practitioner diagnoses of depression from 1,054 individuals enrolled in the Flemish Gut Flora Project. They found specific groups of bacteria that positively or negatively correlated with quality of life; two bacterial genera, Coprococcus and Dialister, were depleted in patients with depression, whether or not they were taking antidepressants. Butyrate-producing bacteria were consistently associated with higher quality of life measures. The findings were replicated in an independent cohort of 1,063 individuals from the Dutch LifeLinesDEEP cohort and in a sample of clinically depressed patients at the University Hospitals Leuven, Belgium. The results provide the first population based evidence for microbiome links with mental health. The microbiology seems to have been conducted to a very high standard, but the study would be of greater importance overall if the phenotyping was more precise and if depression was the primary clinical measure, rather than a combination of quality of life and depression, variables that are related but clearly not equivalent. Despite this reservation the study is a welcome addition to the literature.

If there is a gut dysbiosis in depression, how does this result in the inflammatory phenotype observed in many patients? The answer is simple, we do not know how this comes about. The preclinical findings indicate that the altered microbiota induced by stress is associated with changes in gut permeability which is referred to as a 'leaky gut'(Ohlsson, Gustafsson et al. 2019). If this is the situation in depression, molecules which should not enter the bloodstream such as lipopolysaccharide are enabled to do, triggering an inflammatory response *via* toll-like receptors with an increase in pro-inflammatory cytokines release.

The Jiang et al study is an important watershed that has raised enthusiasm for the view that the gut microbiota might be an integral part of the pathophysiology of depression and as such a potential therapeutic target. The possible interventions might include dietary manipulation, use of beneficial microbes (psychobiotics), use of prebiotics to stimulate growth of beneficial microbes and possibly the use of targeted antibiotics. Under normal physiological circumstances diet is the most important manipulator of the gut microbiota and it is incumbent upon psychiatrists to provide appropriate dietary advice for their patients, an aspect of therapeutic care which is frequently neglected. There is an alarmingly high correlation between poor diet and mental health issues and the gut microbiota is an important variable in this relationship. Clinicians also need to be cognizant of the fact that our current

psychotropics impact the gut microbiota with potential significant side-effects, take for example the effects of atypical antipsychotics on the gut microbiota and the major problem of weight gain in many patients(Davey, Cotter et al. 2013).

While enormous progress has been made in this field over the past decade, we patiently await definitive developments that will impact patient care. Hopefully, the field will not meet the fate of the Beckett characters in Waiting for Godot!

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Figure Legend

Fig. 1 shows the routes of communication between gut microbes and brain together with the channels from brain to gut. Research to date supports the view of a gut dysbiosis in depression. HPA=hypothalamic pituitary adrenal axis; SAM=sympathoadrenal medullary system.

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