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Mental Health and the Brain-Gut-Microbiota Axis: Fundamental Importance of Diet

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Summary

The Mediterranean diet is regarded as the most beneficial diet from a mental health perspective. The benefits of such a diet are mediated significantly through the brain-gut-microbiota axis. Abnormalities in this axis have been described in the most prevalent psychiatric disorders. Individual components of the Mediterranean diet may be beneficial in treating mental health problems. The most extensively studied components include polyunsaturated fatty acids, psychobiotic bacteria, prebiotics and polyphenols. However, more rigorous scientific investigation is required before definitive statements can be made.

The lay public usually view bacteria in a negative light, associated with infective illness. At some stage most of us, have experienced a gut infection that has caused diarrhoea and/or nausea and such infections transiently impact our mood. This is a fact that has been recognised at least from the time of Galen in ancient Rome. In contrast, modern medicine has viewed commensal bacteria in our intestine as harmless and of little benefit. However, it is now becoming clear that certain gut bacteria may positively influence our mood and behaviour. The manner in which they achieve this is gradually being unravelled. The implications of this and the ways in which we can manipulate the gut microbiota are the focus of this chapter.

Background

The brain-gut-microbiota axis is now viewed by many as a novel paradigm in psychiatry and more broadly in neuroscience (Dinan and Cryan 2017). An exponentially accumulating volume of evidence supports the view that gut microbes have a profound impact on central neurochemistry and behaviour, especially stress related responses. How do gut microbes exert such a powerful central influence and how might targeting the brain-gut-microbiota axis yield effective therapies for psychiatric illnesses?

We live in an important interdependent relationship with our microbes. We feed them and in return they produce molecules our bodies require. The total weight of bacteria in our intestines, estimated at 1.5kg, is approximately the same weight as that of our brain. There are far more bacteria in our gut than cells in our body and these bacteria have a vast array of genes. They are capable of producing hundreds, if not thousands of chemicals, many of which influence the brain. In fact, bacteria produce some of the most important brain signalling molecules or neurotransmitters such as dopamine, noradrenaline, serotonin (5HT) and gamma amino butyric acid (GABA) (Wall, Cryan et al. 2014). Furthermore, the brain is predominantly made of fats and many of these facts are produced by the metabolic activity of bacteria. In the absence of gut bacteria brain structure and function are altered, with a significant impact on the mental state and behaviour. In turn, we feed the microbes and different bacteria have differing dietary requirements. Bifidobacteria for instance are enhanced by the intake of complex carbohydrates in the form of prebiotics such as inulin (Fu, Liu et al. 2018).

Component of Brain-Gut-Microbiota Axis

The brain-gut-microbiota axis is a bidirectional communication system which enables gut microbes to communicate with the brain, and the brain in turn to communicate with the gut (Rhee, Pothoulakis et al. 2009). While brain-gut communication has been a subject of investigation for decades, an exploration of gut microbes as a vector within this context has only recently been addressed. The mechanisms of signal transmission are complex and not fully elucidated, but it is clear they include neural, endocrine, immune, and metabolic pathways (Dinan and Cryan 2017). Preclinical studies have implicated the vagus nerve as a fundamental route of communication between gut microbes and centrally-mediated behavioural effects, as illustrated by the elimination of central Lactobacillus rhamnosus effects following full truncal vagotomy (Bravo, Forsythe et al. 2011). Interestingly, it has been demonstrated that individuals who underwent a full truncal vagotomy for treatment of peptic ulcer disease have a decreased risk of certain neurological disorders when they enter old age (Svensson, Horvath-Puho et al. 2015).

The gut microbiota also regulates key central neurotransmitters such as serotonin by altering levels of precursors; for example Bifidobacterium infantis has been shown to elevate plasma tryptophan levels and thus influence central 5-HT transmission (Desbonnet, Garrett et al. 2010). Tryptophan is the precursor of 5HT and the human brain has limited storage capacity, therefore requiring a continual supply from the intestine. Of probable evolutionary significance is the fact many bacteria can synthesise and release neurotransmitters.

For example, Lactobacillus and Bifidobacterium species can produce gamma-aminobutyric acid (GABA): Escheridia, Bacillus and Saccharomyces spp. can produce noradrenaline: Candida, Streptococcus, Escheridia and Enterococcus spp. can produce serotonin: Bacillus can produce dopamine: and Lactobacillus can produce acetylcholine (Lyte 2013, Lyte 2014).

These microbe-produced neurotransmitters can cross the mucosal layer of the intestine, though it is improbable that they directly influence brain function. Even if they enter the blood stream, which is by no means certain, they are incapable of crossing the blood brain barrier (BBB). Their impact on brain function is likely by acting locally on the enteric nervous system. Short chain fatty acids (SCFAs), which include butyrate, propionate and acetate are essential metabolic products of gut microbial activity and may exert central effects either through G-protein coupled receptors, though such receptors are sparsely concentrated in the mammalian brain. They may however act as epigenetic modulators through histone deacetylases (HDACs) (Stilling, Dinan et al. 2014). Immune signalling from gut to brain mediated by cytokine molecules is another well documented route of communication (El Aidy, Dinan et al. 2014). Cytokines produced at the level of the gut can travel via the bloodstream to the brain. Under normal physiological circumstances they do not cross the BBB, but increasing evidence indicates a capacity to signal across the BBB and to influence brain areas such as the hypothalamus where the BBB is deficient. It is through the latter mechanism

the cytokines interleukin (IL)-1 and IL-6 activate the core stress system, the hypothalamic-pituitary-adrenal axis (HPA), bringing about the release of cortisol.

This is regarded as the most potent activating mechanism of the stress system and may be of relevance in conditions such as the depression that emerges with interferon therapy for hepatitis (Capuron, Hauser et al. 2002).

Psychopatholgy and Gut Byosis

There is increasing evidence that some psychiatric and neurological disorders may be associated with a gut dysbiosis.

Depression is the most common mood disorder and globally is the most important of all psychiatric conditions. Dinan and his colleagues studied the gut microbiota in a maternal separation model of depression in rats (O'Mahony, Marchesi et al. 2009). They reported an overactive hypothalamic-pituitary-adrenal axis response in such animals, together with an increase in pro-inflammatory cytokines and a decrease in the diversity of gut microbes.

In a recent study the faecal microbiota was sequenced in a depression study (Jiang, Ling et al. 2015). Forty-six patients with depression and 30 healthy controls were recruited. High-throughput pyrosequencing showed that, according to the Shannon index, increased fecal bacterial alpha-diversity was found in those currently depressed but not in a group who had responded to treatment. Bacteroidetes, Proteobacteria, and Actinobacteria were increased, whereas Firmicutes was significantly reduced.

Despite the profound inter-individual variability, levels of several predominant genera were significantly different between the depressives and controls. Most notably, the depressives had increased levels of Enterobacteriaceae and Alistipes but reduced levels of Faecalibacterium.

The authors conclude that further studies are necessary to elucidate the temporal and causal relationships between gut microbiota and depression and to evaluate the suitability of the microbiome as a biomarker. In our study when rats were given a humanised microbiota from depressed patients as opposed to healthy controls they developed a depressive phenotype from a behavioural and immune perspective (Kelly, Borre et al. 2016). The depressed patients had elevated cortisol output together with decreased faecal microbial richness.

The largest study to date comes from Valles-Colomer et al 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 across the various populations studied was consistent.

Anxiety Disorders

There are no published studies exploring the gut microbiota in any specific anxiety disorder. Of the anxiety disorders, obsessive compulsive disorder (OCD) has been most consistently associated with infection, especially respiratory tract infection with group A beta-hemolytic streptoccus (Lin, Williams et al. 2010). No studies of probiotics in OCD patients have been undertaken, though a rodent study suggests that L. rhamnosus might be effective (Kantak, Bobrow et al. 2014).

Lyte and his colleagues (Lyte, Varcoe et al. 1998) have shown that oral administration of the pathogen Campylobacter jejuni, in subclinical doses, which were too low to elicit overt immune activation, resulted in anxiety-like behaviour in mice. They also reported that areas of brainstem activation, most notably the nucleus tractus solitarius and lateral parabrachial nucleus, participate in neural information processing that lead to autonomic, neuroendocrine and behavioural responses.

In a recently published prospective study Bruch used the Medical Expenditure Panel Survey (MEPS) to assess longitudinally the association between intestinal infection and subsequent onset of an anxiety disorder, through a nationally representative sample (Bruch 2016). Six 2-year panel datasets, each comprised of 5 consecutive rounds, were pooled from 2007 to 2013 to gather records for all respondents 18 years of age or older who did not have an anxiety disorder at baseline (n = 63, 133 people). Within the study sample, there were 2577 individuals with an intestinal infection in Round 1 and 4239 individuals with an anxiety disorder that began in Round 2, 3, 4, or 5. Overall, intestinal infection in Round 1 was associated with a 1.34 ($P < 0.01$) odds ratio of having an anxiety disorder that began in Round 2, 3, 4, or 5. Separate analyses were performed to determine whether the association applied to other infection types, including respiratory infection, urinary tract infection, hepatitis infection, and skin infection. Respiratory infection was associated with a 1.36 ($P < 0.01$) odds ratio of having an anxiety disorder that began in Round 2, 3, 4, or 5; no other infection type showed a significant association. This large scale study provides convincing evidence of a link between intestinal infection and the subsequent development of anxiety.

What is urgently required is a study of the microbiota in patients with anxiety disorders who are appropriately phenotyped, which is not always the case.

Autism

Autism is a neurodevelopmental disorder whose prevalence is apparently on the increase. It is characterised by a failure of language acquisition, obsessional traits and a lack of sociability. It is frequently associated with gastrointestinal symptoms (Li and Zhou 2016), the relevance of which has been a longstanding source of controversy. Up to 70% of patients with the syndrome report abdominal symptoms and hence the view that it is a disorder of the brain-gut axis.

Our group at the APC Microbiome Institute examined the behaviour of mice raised in a germ-free environment (Borre, Moloney et al. 2014, Desbonnet, Clarke et al. 2014). The mice were tested in a three chamber apparatus, where a germ-free mouse was placed in the middle chamber with a familiar mouse in one chamber and a novel mouse in the third. The germ-free mouse spent as much time with the familiar as with the novel mouse; this is in contrast to the behaviour of conventionally colonised mice who spend more time with the novel than the familiar mouse. Germ-free mice are also more likely to spend time with an empty chamber or an object than with another mouse, a decidedly abnormal behaviour for a sociable animal. Colonisation of the germ free mice does partially normalise their behaviour patterns. These behavioural changes are associated with significant alterations in underlying neurochemistry.

Work from Mazmanian's group in an animal model demonstrated that the microbiota modulates behavioural and physiological abnormalities associated with neurodevelopmental disorders such as autism (Hsiao, McBride et al. 2013). They used the maternal immune activation model induced by poly-IC injection during pregnancy and found altered gastrointestinal barrier defects and microbiota alterations. Oral treatment with the human commensal Bacteroides fragilis was shown to correct gut permeability and most interestingly stereotyped and other abnormal behaviours. Furthermore, a metabolite found in the abnormal animals was observed to transfer the phenotype to naïve animals and to be reduced by Bacteroides fragilis.

The faecal microbiota in patients with autism spectrum disorder has been sequenced (Tomova, Husarova et al. 2015). In the most recently published study Tomova et al examined the microbiota in Slovakian children. The faecal microbiota of autistic children showed a significant decrease of the Bacteroidetes/Firmicutes ratio and elevation of the amount of Lactobacillus spp. There was a modest elevation in Desulfovibrio spp and a correlation with the severity of autism. A probiotic diet normalised the Bacteroidetes/Firmicutes ratio and Desulfovibrio spp levels.

As recently summarised by Mayer & colleagues there is a paucity of large comprehensive studies of the microbiome in autism (Mayer, Knight et al. 2014). Again the issue of chicken or egg emerges; are these changes induced by stereotyped diets seen in many individuals as a product of obsessional behaviour patterns? Also the heterogeneous nature of the disease needs to be taken into account and much more effort is needed to tease out the exact role of the microbiome in both the aetiology and treatment of the disorder. Diet is also an important consideration with all microbiota studies in autism.

Schizophrenia

We live in a symbiotic relationship with microbes, and increasing evidence points to the fact that without the activity of these microbes, our social interactions and cognitive functioning would not have evolved to the extent they have. For most sufferers, schizophrenia impacts significantly on these domains.

The protozoa Toxoplasma gondii is known to cause major perturbation to the gut microbiota (Molloy, Grainger et al. 2013) and is a recognized environmental risk factor for schizophrenia (Bhadra, Cobb et al. 2013). In rodents it is capable of altering host behavior and underlying anxiety levels (Vyas, Kim et al. 2007). Recent studies in healthy elderly indicate that latent infection can lead to deficits in goal directed learning with alterations in dopaminergic neural transmission (Beste, Getzmann et al. 2014). Cases of schizophrenia have been associated with C. difficile infection and reported as mediated by a phenylalanine derivative produced by the bacteria (Shaw 2010). There are no prospective studies available on the outcome of otherwise healthy babies who have colonised this organism.

It has been argued that any genomic analysis in the disorder should include an analysis of gut microbial DNA (Dinan, Borre et al. 2014) and a recent preliminary study investigated differences in faecal microbiota between 28 patients with first-episode psychosis (FEP) and 16 healthy matched controls and explored whether such differences were associated with response after up to 12 months of treatment (Schwarz, Maukonen et al. 2018). Numbers of Lactobacillus group bacteria were elevated in FEP-patients and significantly correlated with severity along different symptom domains. A subgroup of FEP patients with the strongest microbiota differences also showed poorer response after up to 12 months of treatment.

Psychobiotics

Metchnikoff , a Nobel laureate, was the first to observe the fact that those living in a region of Bulgaria who consumed fermented food in their diet tended to live longer. He first published his observations in 1908 and this gave rise to the concept of a probiotic or bacteria with a health benefit. That bacteria might have a positive mental health benefit is now becoming clear. Such bacteria may influence the capacity to deal with stress, reducing anxiety, perhaps positively impacting on mood and are now called psychobiotics. Whether, they are capable of acting-like and in some circumstances replacing antidepressants remains to be seen. At a time when antidepressant prescribing has reached exceedingly high levels, the emergence of effective natural alternatives, free from side-effects, would be welcome.

Psychobiotics are health benefitting bacteria which when ingested in adequate amounts have a mental health benefit (Dinan, Stanton et al. 2013, Bambury, Sandhu et al. 2018).

The mechanisms of psychobiotic action are gradually being unravelled. It has been show that Lacobacillus rhamnosus has potent anti-anxiety effects in animals and does so by producing major changes in the expression of GABA receptors in the brain. GABA is the most important inhibitory transmitter in the human brain and these are the receptors through which benzodiazepines such as diazepam and various anaesthetic agents act. The changes in these receptors are mediated by the vagus nerve which connects the brain and gut. When this nerve is severed no effect on anxiety or on GABA receptors is seen following psychobiotic treatment. An impact on obsessive compulsive disorder type symptoms has also been reported with a similar strain of psychobiotic. Interestingly, Lacobacillus rhamnosus not only alters GABA receptors in the brain but has been shown to synthesise and release GABA. There is also evidence to support the view that gut bacteria may influence the brain in routes other than the vagus nerve, for example by immune modulation and by the manufacture of tryptophan and short chain fatty acids.

Just as certain genes render bacteria pathogenic, it is likely that clusters of genes provide mental health benefits. The essential genes for effective psychobiotics have yet to be established. It may be that at some stage in the future the ideal psychobiotic will be a genetically modified organism containing genes from several different bacteria. In the meantime, cocktails of bacteria may be more effective than single strains in producing health benefits. A recent study compared treatment with a combination of Lactobacillus helveticus and Bifidobacterium longum versus placebo in healthy subjects on a range of psychological measures. Daily administration of the psychobiotic combination significantly reduced psychological distress in the form of anxiety and depressive symptoms. The study also looked at the impact on the key stress hormone cortisol and found that the urinary free excretion of this hormone was reduced by the psychobiotics. The study strongly suggests that the combination of the two bacteria reduce both the psychological and biological impact of stress in healthy individuals. Another study found that a Bifidobacterium longum strain significantly altered stress responses(Allen, Hutch et al. 2016). In a clinical setting, it has been shown that some but not all psychobiotic bacteria impact on the symptoms of irritable bowel syndrome, a common stress-related disorder of the brain-gut axis. They probably do so by reducing blood cortisol levels and inflammatory cytokine molecules.

Diet and the Microbiota

Over recent decades, dietary patterns in Europe and elsewhere have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. This 'Westernization' of diets together with sedentary lifestyles results in modifications to the gut microbiota, which may at least partially contribute to the increasing incidence of chronic inflammatory disorders, such as cardiovascular disease, obesity, inflammatory bowel disorder and depression (Galland 2010). If we are to improve the nutritional value of food and positively impact mental health, we need to more fully understand the biological interactions between the food and microbiota. Many human studies have assessed dietary impact on the gut microbiota but they are limited by the difficulties in controlling potential confounding variables especially lifestyle behaviours. Studies are limited by the fact that the microbiota is sequenced from faecal samples which provides no detail of the microbiota in various gut regions. With these limitations in mind we have learned some useful lessons in relation to dietary patterns and microbiota composition.

Mediterranean Diet and Depression

There is increasing evidence to support the view that poor quality diet is a risk factor for major depression. Epidemiological studies have long demonstrated that those on a Mediterranean diet suffer from less depression (Sanchez-Villegas, Henriquez et al. 2006). Diets rich in fruit, vegetables, grains and fish seem protective against depression while a diet of highly proceeded food and those with a high sugar content predispose to depression(Akbaraly, Brunner et al. 2009). However, the data upon which these conclusions are based are largely observational. There is a paucity of properly controlled studies.

A recent study from Australia used a randomized controlled trial (RCT) design to investigate the efficacy of a dietary program for the treatment of major depression(O'Neil, Berk et al. 2013). A structured dietary support, focusing on improving diet quality using a modified Mediterranean diet was compared to a social support control condition. Sixty-seven patients were recruited fulfilling criteria for major depression and scoring 75 or less, out of a possible score of 104, on a Dietary Screening Tool, a score which indicated a poor baseline diet. If patients were on antidepressant medication or undergoing psychotherapy, they were required to be on the same treatment for at least 2 weeks prior to study entry. The dietary intervention group showed a significantly greater improvement in depression scores between baseline and 12 weeks than the social support control group. Overall, the results of this trial suggest that improving diet may be a useful strategy for treating depression or at least as an adjunctive to conventional therapies. Another study by Forsyth and colleagues reaches similar conclusions(Forsyth, Deane et al. 2015). Furthermore, evidence is accumulating to support the view that the way in which diet impacts health in general is mediated by the gut microbiota(De Filippis, Pellegrini et al. 2016, Haro, Garcia-Carpintero et al. 2017).

If we assume that a Mediterranean diet is effective in the prevention and perhaps the treatment of depression, what components of such a diet mediate these effects?

Polyunsaturated Fatty Acid and Mood

The brain is a lipid-rich organ containing mostly complex polar phospholipids, sphingolipids, gangliosides and cholesterol (O'Brien and Sampson 1965). These are involved in both the morphology and physiology of neurones. The glycerophospholipids in the brain contain a high proportion of polyunsaturated fatty acids (PUFA) derived from the essential fatty acids, linoleic acid and alpha-linolenic acid. The main PUFAs in the brain are docosahexaenoic acid (DHA) derived from the omega 3 fatty acid, alpha-linolenic acid, and arachidonic acid and docosatetraenoic acid, both derived from the omega 6 fatty acid, linoleic acid(Haag 2003).

Omega-3 fatty acid is derived from fish oil and there is considerable epidemiological evidence to indicate that those with a diet rich in fish have a lower incidence of cardiovascular disease than those with other diets(Sakai, Ishida et al. 2017). In recent times, the focus of attention has been on the impact of omega-3 fatty acids on depression. Studies indicate that in countries where there is a high consumption of fish there are lower rates of depression(Li, Liu et al. 2016). However, in many European countries in recent decades the intake of omega-3 PUFAs has declined with a concomitant increase in omega-6 PUFA intake(Simopoulos 1999). Hibbeln was one of the first to draw demonstrate the importance of omega-3 PUFAs in mental health: in a cross-national study he found a significant negative correlation between worldwide fish consumption and prevalence of depression (Hibbeln 1998). Subsequent studies have found altered omega-6/omega-3 ratios in the plasma of depressed patients (Dinan, Siggins et al. 2009) and altered red blood cell phospholipids (Peet, Murphy et al. 1998). In post-mortem brain tissue lower DHA levels have been found in the orbitofrontal cortex of in depressed patients.

Nemets and colleagues studied 22 depressed patients who failed to respond to antidepressant therapy(Nemets, Stahl et al. 2002). The study had a parallel group, double-blind design in which EPA or placebo was added to the on-going antidepressant. A significant effect of omega-3 compared with placebo was found by week three of treatment. Peet et al examined the effects of EPA in 70 patients who had antidepressant resistant depression (Peet and Horrobin 2002). Patients were randomised to receive either placebo or EPA in doses of 1, 2 or 4 grams per day for 12 weeks. They continued their antidepressant throughout. Forty-six of the 52 patients receiving the EPA and 14 of the 18 patients receiving placebo completed the 12 weeks study. The 1 gram per day group showed a significantly better outcome than the placebo group. The authors conclude that EPA 1 gram per day is an effective strategy for augmenting antidepressants in those who are treatment resistant.

The results with DHA are inconclusive. Thirty-six subjects with major depression assigned to receive DHA (2 g/d) for 6 weeks did not show differences in the score of the Montgomery-Asberg Depression Rating Scale compared with the placebo-treated group (Marangell, Martinez et al. 2003). A number of open label studies without appropriate controls report benefits. Given the lack of a placebo control, these results need to be viewed with caution (Smith, Sarris et al. 2017).

A recent meta-analysis of fifteen trials (916 total participants) using omega-3 PUFAs as either a mono or adjunctive therapy were analysed. Studies were selected based on prospective, randomized, double-blinded, placebo-controlled study design, if depressive episode was the primary complaint with or without comorbid medical conditions and, if appropriate outcome measures were used to assess depressed mood (Sublette, Ellis et al. 2011). This meta-analysis concluded that n-3 PUFA supplements with >60% of EPA (in a dose range of 200 to 2200 mg/d in excess of DHA) ameliorated the clinical condition. However, doses containing primarily DHA or <60% EPA were not effective against primary depression.

It is known that EPA has a general immuno-suppressive effect with a capacity to suppress inflammatory states. This may be relevant in the context of depression which is known to be associated with an increase in the acute phase protein C-reactive protein (CRP) and pro-inflammatory cytokines. A recent study demonstrated the capacity of polyunsaturated fatty acids to impact the brain-gut axis by increasing levels of bifidobacteria (Costantini, Molinari et al. 2017). At this point it seems reasonable to recommend fish in the diet of patients with depression but there is insufficient data to recommend omega-3 PUFAs as either a mono or adjunctive therapy in the disorder.

Probiotics and Depression

Fermented foods have long been associated with a health benefit but only recently has that benefit been extended to mental health. Numerous claims of therapeutic efficacy have been made for probiotics but most claims are not substantiated by rigorous placebo controlled studies. Psychobiotics are defined as bacteria which when ingested in adequate amounts have a positive mental health benefit (Dinan, Stanton et al. 2013).

One therapeutic area where the benefits of probiotics have been established is in the common gastrointestinal disorder IBS. Several placebo controlled studies indicate that a bifidobacteria is highly effective in treating the condition(Quigley 2018). This is of relevance given the fact that up to 40% of patients with IBS have co-morbid depression and many bifidobacteria have anti-inflammatory activity.

The principal rationale for the use of probiotics in treating major depression rests on their potential for suppressing the pro-inflammatory component of depression. Can probiotics/psychobiotics alter this aberrant immunology? It was shown that a bifidobacteria in IBS switched the balance from a pro- to an anti-inflammatory cytokine response (O'Mahony, McCarthy et al. 2005). They found that in response to bifidobacteria treatment there was an increase in anti-inflammatory IL-10 and a reduction in pro-inflammatory IL-12 activity. Similar findings have been reported with Lactobacillus acidophilus (Torii, Torii et al. 2007).

There are several animal models of depression used for drug development. Using the maternal separation model, Bifidobacterium longum 35624 was found to normalise behaviour (Desbonnet, Garrett et al. 2010) and reduce corticosterone levels. This may indicate that the specific bifidobacteria strain has an antidepressant action.

In a recent study, Benton and colleagues used a placebo controlled design to examine the impact of probiotics on mood in healthy community based subjects. One-hundred and thirty-two subjects with a mean age of 62 years were recruited(Benton, Williams et al. 2007). Over a three week period they consumed either milk containing a probiotic or placebo daily. Mood was assessed at baseline and after 10 and 20 days of treatment. Those who rated their mood as poorest at baseline reported on average an improvement on probiotic by the end of the study. This improvement was not noted on placebo. Whether these findings translate to a clinical sample remains to be seen.

The effects of Lactobacillus rhamnosus HN001 given in pregnancy and postpartum on symptoms of maternal depression and anxiety in the postpartum period was assessed (Slykerman, Hood et al. 2017). Two hundred and twelve women were randomised to HN001 and 211 to placebo. Women who received HN001 had significantly lower depression and anxiety scores in the postpartum period. The results strongly support the view that the psychobiotic is protective against the emergence of postpartum symptoms. This is the best human intervention study so far in the literature. Overall, it seems reasonable to conclude that psychobiotic studies in depressed patients are urgently required.

Prebiotics and Depression

Prebiotics are fibres metabolised by the microbiota and capable of increasing the levels of good bacteria such as bifidobacteria. Prebiotics are found in vegetables such as celery, Jerusalem artichoke, garlic etc. A number of small clinical controlled trials have assessed the efficacy of certain prebiotics on psychological outcomes with promising results. Schmidt and colleagues demonstrated that 3-week supplementation with a galactooligosaccharide (GOS) prebiotic, which has been shown to stimulate bifidobacterial growth, in healthy volunteers significantly reduced waking cortisol response, the stress hormone strongly linked to anxiety and depression (Schmidt, Cowen et al. 2015). Moreover, a B-GOS cohort demonstrated altered behavioural outcomes through a decrease in attentional vigilance to negative versus positive information in a dot-probe task compared to placebo. It is interesting to note, however, that fructooligosaccharide (FOS) supplementation had no effect. These results suggest that shaping of microbiota composition through prebiotic intake could influence behavioural outcomes. In humans, prebiotic supplementation with trans-GOS not only enhanced bifidobacterial growth and improved bloating symptoms, but in addition significantly reduced anxiety scores in IBS sufferers (Silk, Davis et al. 2009).

Polyphenols

Polyphenols are undoubtedly the most numerous among the groups of phytochemicals present in plants. They are broadly divided into flavonoids and non-flavonoids. Resveratrol which is found in red wine has potent CNS actions. In an animal model of depression it has been shown to reduce depressive type behaviours while attenuating the release of both corticosterone and pro-inflammatory cytokines (Yang, Song et al. 2017). It also exerts anti-oxidant activity acting through sirtuins, is known to be metabolised by the microbiota and influences the Firmicutes/Bacteroidetes ratio in the intestine (Bird, Raederstorff et al. 2017). To date there are no published controlled trials of resveratrol in depressed patients.

The polyphenol natural product curcumin possesses a variety of biological and pharmacological properties. Curcumin was found to reduce salivary cortisol levels in depressed patients relative to that seen in the placebo group(Yu, Pei et al. 2015). Recent data also indicates an impact in increasing gut microbial diversity (Zhang, Chen et al. 2017).

Dietary Recommendations

The MyNewGut EU funded consortium recently published recommendations on diet for optimal mood states(Dinan, Stanton et al. 2018). They recommend that patients with depression or vulnerability to depression should be encouraged to enhance a plant-based diet with a high content of grains and fibres. They also recommend a decreased consumption of red meat, especially of processed meat(Oddy, Allen et al. 2018), a regular intake of fish(Thesing, Bot et al. 2018) and fermented foods(Selhub, Logan et al. 2014). The intake of sodium and refined sugar should be restricted. Vigorous aerobic exercise consistent with the age and physical health of the patient should be encouraged(Stubbs, Vancampfort et al. 2018).

Conclusions

There is an ever-increasing volume of data to support the view that the gut microbiota plays a fundamental role in regulating brain physiology and behaviour. A gut dysbiosis is now viewed by many as a fundamental disturbance in some forms of mental illness, especially depression. If this is the case, addressing the dysbiosis using dietary strategies may be of major benefit to patients. Components of the Mediterranean diet undoubtedly almost certainly positively impact mental health. However, a more rigorous investigation of the individual components is required. This will require appropriate clinical trials.

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