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WILEY BIPOLAR DISORDERS

COMMENTARY

Targeting the gut to achieve improved outcomes in mood disorders

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The field of what is referred to as Nutritional Psychiatry[1] is gaining traction, with increasing interest from scientists, clinicians, and the wider public. Although less than 10 years since the publication of the first studies showing that habitual diet quality is linked to the risk for depression independent of relevant factors such as education, income, body weight, and other health behaviours, and not apparently explained by reverse causality, there are now several meta-analyses confirming these associations across countries and age groups. More recently, two randomised controlled trials have demonstrated the apparent efficacy and cost effectiveness of dietary support for the treatment of depression; these trials utilised a Mediterranean-style diet as treatment. This diet emphasises the consumption of nutrient and fibre-rich plant foods including fruits, vegetables, wholegrain cereals, legumes, and nuts and seeds, as well as olive oil and fish, and the avoidance of foods high in saturated and trans fats, added sugars and salt. The benefits of Mediterranean diet to chronic disease is well established and given the high level of comorbidity between diet-mediated chronic diseases such as obesity and mood disorders,[2] the fact that dietary quality is closely linked to depression risk and that improving diet can also improve depression is perhaps not surprising. However, there is a clear need to understand and describe mechanisms of action linking diet to mental and brain health in order to add credence to the evidence base and to develop targeted interventions for both prevention and treatment.

Reviews and discussions of such mechanisms have previously focused on the established influence of diet on immune function and neuroplasticity, both of which are of relevance to mental health. However, further impetus to the field has been provided by the recent understanding of the likely importance of the gut and its resident bacteria to mental and brain health. The evidence for the role of gut bacteria in modulating brain health and behaviour is extensive, although derived mainly from preclinical research to date. Gut bacteria synthesise and influence the synthesis of neurotransmitters including GABA, noradrenaline, acetylcholine, serotonin, and dopamine; although these are not expected to cross the blood brain barrier, gut bacteria directly affect tryptophan availability and thus central serotonin levels by influencing host enzymes responsible for its degradation. Mice bred without commensal bacteria (germ-free mice) have pronounced changes to their stress response system, brain plasticity, immune function, blood-brain barrier integrity, neurotransmitter levels, and behaviour. Administration of probiotic bacteria can attenuate behavioural despair in adult rats exposed to early life stress, as well as normalising immune response and restoring noradrenaline concentrations. Perhaps most remarkably, transfer of microbiota via faecal transplant can transfer behavioural phenotypes in mice, while faecal transplants from human donors with depression can induce a depressed phenotype in microbiota-depleted rodents.[3] In humans, a very recent randomised controlled trial in patients hospitalised with acute mania has shown that those receiving adjunctive probiotic bacteria had a longer time to rehospitalisation and fewer days spent in hospital than those receiving placebo.[4] This supports the potential of targeting the gut to achieve improved outcomes in people with mental disorders.

The primary role of gut microbiota is the metabolism by fermentation of dietary fibre found primarily in plant foods such as fruits and vegetables, wholegrains, and legumes. The metabolites produced by the fermentation process include short-chain fatty acids (SCFAs), which interact directly with cells throughout the body via G-protein coupled receptors. SCFAs have profound immunomodulatory properties, regulate the release of gut peptides

from enteroendocrine cells, which in turn affect gut-brain hormonal communications, increase mitochondrial activity, and regulate the synthesis of gut-derived 5-HT from enterochromaffin cells. They affect gene transcription, including epigenetic mechanisms via acetylation and deacetylation of histone proteins and the activity of transcription factors. The bacterial SCFA butyrate, the production of which is increased on consumption of host-indigestible carbohydrates (dietary fibre), has anti-inflammatory effects and is important for maintaining the intestinal barrier by increasing the number of tight junctions within the epithelial layer of the colon. This may be of relevance to depression, where inflammation is a known determinant and there is evidence of translocation of bacteria into the bloodstream with associated immune responses.[5]

Given the apparent importance of the gut microbiota to the brain and multiple biological pathways related to the risk for mood disorders, and the current understanding that diet is a primary determinant of gut microbiota composition and function, interventions targeting the gut through the use of dietary strategies that promote fibre-rich foods have potential and, if the next generation of definitive studies holds up, will be warranted; such interventions are also likely to have wider benefits to physical health and the healthcare burden. The updated clinical practice guidelines for mood disorders nominate supporting a healthy diet, as well as sleep hygiene, increased physical activity and substance cessation, as key strategies in the management of major depressive disorder. However, many clinicians feel currently ill-equipped to offer guidance on diet. Until medical training includes a focus on nutrition that is commensurate with the fact that poor diet is now the leading cause of early mortality in middle and high-income countries, referral to clinical dietitians for patients with mood disorders may be a useful strategy in tandem with first-line treatments.

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