The gut-brain axis and microbial therapeutics: The future of personalized medicine for psychiatric disorders

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Abstract:

Given the vast personal and economic burdens of psychiatric disorders, specifically mood and anxiety disorders, finding appropriate treatments for all those affected is critical. Due to the various presentations of psychiatric indications, no one treatment method is efficacious in all patients. Thus, a more personalized, but feasible treatment method is necessary for properly treating and preventing these disorders from becoming refractory and more burdensome. In recent years, there has been a growing appreciation for research in the field of the "gut-brain axis" (GBA), specifically as a target for psychiatric disorders. Researchers have found the gut to be influenced not only by similar determinants to that of psychiatric indications, but also highly modifiable using GBA treatments such as probiotics and fecal microbiota transplant (FMT). This is compelling evidence for the use of the GBA as a target for disorders such as depression and anxiety and for development of personalized treatment methods.

Mental illness can be considered similar to other physical illnesses in that it has a wide variety of causes and symptoms; however, it's not quite as straightforward in its etiology. Mental illness refers to a broad range of mental health conditions that affect feelings, thoughts, and as a result, behaviour. On average, 1 in 5 Canadians experience a mental illness or addiction problem, with 70% of the mental health problems beginning in childhood or adolescence [1]. Mood and anxiety disorders are among the most prevalent mental illnesses and due to overlapping symptoms and causes, they can often be comorbid with one another, further complicating disease presentation and course. In addition to psychiatric symptoms – such as depressed mood, loss of interest, and excessive worry – mood and anxiety disorders are characterized by significant functional impairments in affected individuals [2]. There are great personal and economic burdens associated with these indications, yet effective treatments that work for all those affected remain unknown. This is partly due to high individual variability in symptoms and course, comorbidity with other psychiatric and non-psychiatric disorders, and the influence of genetic and environmental factors.

Traditionally, we have been drawn to the physiological causes of illnesses, however understanding mental health requires condering both the physiological and environmental causes in conjunction with one another. The main physiological cause of mood and anxiety disorders is believed to be an imbalance of neurotransmitters, such as serotonin and norepinephrine. Serotonin and norepinephrine are both involved in the regulation of emotions and cognition, among many other functions [3,4]. This explains the theory behind selective serotonin and serotonin-norepinephrine reuptake inhibitors as treatments for many psychiatric disorders as they enhance neurotransmission of serotonin and norepinephrine by increasing their availability in the brain by delaying their reuptake [5].In addition to these physiological mechanisms, there exists a wide range of environmental determinants that may also influence the development of psychiatric disorders, such as socioeconomic status, diet, traumatic life events, and adverse childhood experiences; however these factors are not always considered when developing treatments. Given the heterogeneity that exists in mental disorders, efforts to comprehensively understand, prevent, and treat mental illness will require a more holistic approach – perhaps one that explores multiple targets for treatments on a case-by-case basis.

Current treatments for psychiatric illness

Standard options for treating most psychiatric illnesses include antidepressant medication and/or psychotherapy. Other treatment methods, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and ketamine are also options. Although ample amounts of research have been conducted on antidepressant treatment options to unveil highly efficacious pharmacological interventions, as it stands, they tend to have many side effects, unwanted pharmacological actions, and are not as easy to personalize [6,7]. This can

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therefore make antidepressants a poor first-line treatments for some individuals [8]. As for psychotherapy, although also highly effective and more personalized to focus on the individual's thoughts and actions, it can be rather expensive and often associated with long waitlists to receive care. Further, treatments such as ECT, TMS, and ketamine are often administered in later stages of depression, to those that are often resistant to pharmacotherapy, making them less of a preventative treatment method. ECT also requires hospital equipment and anesthesia and may be associated with side effects such as cognitive impairment [9]. Ketamine, although also highly efficacious, can cause dissociation, may have high addictive potential and is often abused as a recreational drug [10]. This highlights a need for more preventative, personalized, and feasible treatment methods.

Gut-brain axis: A novel target for mood and anxiety disorder

In recent years, there has been a growing appreciation for research in the field of the "gut-brain axis" (GBA), specifically as a target for psychiatric disorders. The GBA consists of bidirectional, biochemical, and neural signalling between the gastrointestinal (GI) tract and the brain [11]. The GI tract is colonized by over one hundred trillion commensal bacteria that exist symbiotically with our bodies and is largely influenced by mode of delivery (c-section vs. vaginal birth) and through breast feeding [12].

The human gut microbiota is known to have substantial individual variability in bacterial abundance and diversity and is influenced by a variety of factors such as genetics, diet, metabolism, age, geography, antibiotic treatment, and stress [13]. Although similarities exist in the gut microbiome of different individuals, no two individuals have the same gut microbiota composition [14]. However, in recent studies, individuals with psychiatric disorders have been shown to have a significantly dissimilar microbiota composition compared to healthy individuals, due to decreased diversity and abundance of the healthy gut microbes [15].

The gut microbiota is able to modulate the GBA both directly and indirectly via endocrine, neural, metabolic, and immune pathways; these pathways can become compromised in disease- or stress-states resulting in intestinal dysbiosis; changes in mood, behaviour, and cognition; and altered inflammatory levels [16]. During stress states, our hypothalamic-pituitary-adrenal (HPA) axis is activated and a release of hormones – such as corticotropin releasing factor, adrenocorticotropic hormone, and cortisol – ensues in response to stress. Beginning at the HPA axis, communication between the brain and intestinal lumen of the GI tract is facilitated by the GBA. The gut microbiota alters the availability of nutrients and release of peptides. Galanin, a neuropeptide that is involved in sleep/wake regulation, feeding, mood, and nociception is an example of one of these peptides. Via HPA axis stimulation, galanin influences the release of the above mentioned hormones, suggesting a potential role in stress modulation [17]. The release of cortisol can affect immune cells, alter enteric muscles and gut permeability, and change microbiota composition [10].

The immune pathways consist of immune cells located in the gastrointestinal tract to facilitate proper functioning of the gut. One of their functions is to release signaling proteins known as cytokines (such as the interleukins IL-10 and IL-6). During disease-states, cytokines interact with other immune cells to regulate the body's immune response. When the gut microbiome is altered, the number of inflammatory cytokines can be affected, leading to dysregulated enteric nervous system, increased gut epithelial permeability, and activated pain sensory pathways. These disruptions can trigger low-grade inflammation, commonly seen in stress-related psychiatric illnesses [17].

The neural pathway of the GBA involves the vagus nerve, enteric nervous system, and the activity of the neurotransmitters. The afferent nerve fibers of the vagus nerve, gather information from metabolites of the microbiota, immune cells, and enteric muscles and communicate it to the central nervous system [16-18]. The central and peripheral changes that occur as a result of this communication are hypothesized to improve psychiatric symptoms.

Finally, the metabolic pathway mainly involves metabolites produced by gut microbiota via fermentation of non-digestible carbohydrates. These metabolites are known as short-chain fatty acids (SCFA). Though indigestible, these SCFAs are integral for the gut to carry out various roles through interactions with the gut microbiome. In particular, they influence the synthesis of the rate-limiting enzyme tryptophan hydroxylase which synthesizes serotonin produced by enterochromaffin (EC) cells [19, 20]. Approximately 90% of the body's serotonin is produced by EC cells [21]. In the gut, SCFAs also influence the expression of anti-inflammatory markers, such as IL-10, in macrophages and intestinal dendritic cells [22].

The interaction of the gut with the aforementioned environmental determinants of psychiatric illnesses – such as diet and early life stress and the pathways connecting the gut and brain – indicate that the gut microbiome may be a good target to prevent and treat psychiatric symptoms.

Gut-repopulation treatments: Potential for personalization

In current research, repopulating and strengthening the gut with the use of GBA treatments are being explored to determine the influence of the gut microbiome on the gut-brain axis. There exists two distinct GBA treatment methods that are more heavily explored than others – probiotic treatments and fecal microbiota transplants. While probiotic treatments are used to supplement the gut with one or two healthy bacterial strains, fecal transplant is the transfer of many strains of fecal bacteria from a healthy donor to a recipient [23]. These treatments aid in upholding the bacterial balance and function. Other variations of this treatment, such as Microbial

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Ecosystem Therapeutics-2 (MET-2), are also currently being explored in psychiatric indications such as Generalized Anxiety Disorder and Major Depressive Disorder. MET-2 consists of gut bacteria from a healthy donor, chosen for its safety profile, that is then purified from stool samples and lab-grown prior to being lyophilized and ingested orally by patients [24]. Current research, particularly studies exploring the use of FMT for psychiatric illness, suggest an improvement in mood or anxiety symptoms in both preclinical and clinical populations[25]. A recent review by Chinna Meyyappan et al. systematically weighs the pros and cons of FMT [25]. Though every study found an improvement in psychiatric symptoms which may be mediated by gut repopulation and improvement of GI symptoms, there are limitations. These include transiency of treatment effects; unknown costs and associated stigma; and lack of large-scale, double-blind, placebo-controlled trials, given the novelty of the treatment method. The studies also differed in many aspects including FMT administration protocols, main indications (chronic stress, anorexia, depression), and underlying GI conditions, which makes it hard to draw overarching conclusions [25]. Probiotics studies, have also found positive results with similar drawbacks [26, 27].

A therapeutic advantage to the link between psychiatric disorders and the gut microbiota is the accessibility and modifiability of the gut. Prior to administering aforementioned GBA treatments, stool samples are often obtained from patients. These samples are analyzed for diversity and abundance of bacteria and can show the dissimilarities between healthy patients and patients with psychiatric disorders. As we learn more about what makes a "healthy" microbiome, we can use this baseline data to personalize treatments such as MET-2 to include bacterial strains that are lacking in ill participants when compared to what we define as a healthy microbiome. Although studies looking into the efficacy of microbial ecosystem therapeutics in alleviating mood and anxiety symptoms have yet to be published [24], ongoing research exploring the use of other GBA treatments, such as fecal microbiota transplant (FMT) and probiotics, suggest there is great potential for personalization [25, 26].

Due to the many influencers of gut microbiome and as a result incredible variability between individuals, the gut may be a good representation of individual history. Given the connection between the gut and psychiatric symptoms, detailed analyses of the gut could therefore explain the differences in risk of illness, disease course, and response to treatment. Additionally, the similarity between the environmental determinants of gut composition and psychiatric disorders indicate that the GBA may be an excellent target for treatments. Due to the varied presentations of these indications, personalized medicine approaches are critical for not only treating and managing them, but also for preventing the illnesses from becoming refractory. Thus, the modifiability of the gut using GBA treatments, such as MET-2, shows its potential as a personalized treatment method for psychiatric symptoms.

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