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Beyond the neuro-immune interplay in depression: Could gut microbes be the missing link?

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ABSTRACT

Accumulating evidence have positioned inflammatory signaling pathways as crucial routes by which microbes inhabiting the gastrointestinal tract (the gut microbiota) communicate with the host brain to influence behavior, with impacts on mental illnesses. In this short review, an overview of inflammatory and gut microbiota status in human depression and in rodent models of the illness are provided. Next, potential inflammatory pathways mediating the communications between the gut and the brain under stressful conditions are described. Finally, dietary interventions targeting the gut microbiota-immune-brain axis in the context of depression are briefly discussed.

1. Introduction

Inflammatory molecules are now recognized as key contributors to the pathogenesis of major depression, likely owing to their actions on brain processes involved in stress responsiveness and resilience (Enache et al., 2019; Hodes et al., 2015; Osimo et al., 2020). Appreciable evidence suggest that inflammatory disturbances seen in depression could stem from pro-inflammatory shifts in microbial communities inhabiting the gastrointestinal tract, referred to as the gut microbiota (Audet, 2019; Dinan and Cryan, 2017; Forsythe et al., 2016; Foster et al., 2017). The observation that microbiota colonization of the gastrointestinal tract, maturation of the immune system, and development of the brain overlap at crucial stages of development further points to the possibility that these processes may start to influence each other early during development (Jasarević et al., 2016), leading to the establishment of a dysfunctional gut microbiota-immune-brain axis and of abnormal behavioral patterns in the face of environmental insults (e.g., stressors). In this review, an up-to-date overview of inflammatory and gut microbiota status in human depression and in rodent models of the illness will first be provided. Next, potential inflammatory pathways mediating the gut-brain crosstalk as well as their establishment and maintenance in stressful conditions will be described. Finally, the use of dietary interventions targeting the gut microbiota-immune-brain axis for depression will be briefly discussed.

2. The gut microbiota-immune-brain axis and depressive illnesses

A growing body of evidence suggest that perturbations to the signaling of key inflammatory molecules between gut microbes and the host brain (the gut microbiota-immune-brain axis), either caused by psychological stressors or by other immunogenic insults, could promote the development and maintenance of depressive phenotypes (Dinan and Cryan, 2017; Foster et al., 2017; Kelly et al., 2015). The contribution of inflammatory factors to depression has been consistently confirmed by several meta-analyses showing that non-medicated individuals with major depression had higher circulating concentrations of pro-inflammatory cytokines (signaling molecules between immune cells), particularly of interleukin (IL)-6 and tumor necrosis factor (TNF)-α (Dowlati et al., 2010; Köhler et al., 2017; Liu et al., 2012; Osimo et al., 2020). The capacity of interferon (IFN)-α to elicit a syndrome similar to that of major depression in patients with hepatitis C or some types of cancer also supports a role, more causal in this instance, for pro-inflammatory factors in depression (Capurro and Miller, 2004; Musselman et al., 2001). More recently, the use of chimeric antigen receptor T-cell therapy in the treatment of hematological malignancies was similarly reported to promote depressive symptoms, potentially because of the cytokine release syndrome these patients experienced post-therapy (Dai et al., 2021). Although fewer studies exist in this regard, markers of...
brain inflammatory activation have been reported in individuals with major depression. Higher cerebrospinal fluid levels of IL-6 and up-regulated post-mortem brain expression of TNF-α and of other cytokine transcripts were detected in individuals with major depression (Dean et al., 2010; Sasayama et al., 2013; Shelton et al., 2011), along with an elevated density of the translator protein (a marker of increased activity of microglia, the brain immune cells) in different regions of the brain (Holmes et al., 2018; Richards et al., 2018; Setiawan et al., 2015). Notably, some of the peripheral and central inflammatory markers in depressed individuals were linked with symptom severity (Calarge et al., 2019; Setiawan et al., 2015), suggesting that higher inflammatory activation in depression could reflect more severe states of the illness.

One research avenue that we and others have been pursuing is the possibility that the increased inflammatory activation in circulation and in the brain of individuals with depression could originate from impairments at the intestinal barrier that would allow bacterial fragments to translocate into the bloodstream, leading to an extra-intestinal inflammatory cascade (Kelly et al., 2015; Maes et al., 2008). A clear picture of the microbiota components altered by a depression has yet to be established (Dinan and Cryan, 2017), but available reports suggest that compositional differences in gut bacterial communities in individuals with depression may be reflective of a pro-inflammatory intestinal environment (Chen et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Valles-Colomer et al., 2019; Zheng et al., 2016). In line with this view, individuals with major depression had higher levels of Proteobacteria and of Enterobacteriaceae, which are mainly composed of Gram-negative bacteria capable of producing the endotoxin lipopolysaccharide (LPS) (Jiang et al., 2015). They also had lower levels of Faecalibacterium (Chen et al., 2018; Jiang et al., 2015; Zheng et al., 2016), and levels of this anti-inflammatory genus were negatively correlated with depression severity (Jiang et al., 2015) and positively correlated with quality of life indicators (Valles-Colomer et al., 2019). Markers of intestinal permeability (e.g., urinary lactulose to mannitol ratio, plasma levels of intestinal fatty acid binding protein) and of bacterial translocation (e.g., plasma levels of the 16S rDNA subunit of gut microbiota) were also higher in non-medicated individuals with depression and/or correlated to symptom severity (Calarge et al., 2019; Kéri et al., 2014; Ohlsson et al., 2019), adding support to the view that fragments from a pro-inflammatory microbiota could cross an impaired intestinal barrier and initiate extra-intestinal inflammation in the context of depression. Curiously, however, it appears that higher levels of inflammatory markers in the brain were not strongly correlated with those in circulation (Enache et al., 2019). Whether brain inflammatory activation in depression results from higher circulating cytokines is still not entirely clear, although a decreased expression of the tight junction protein claudin-5 (Menard et al., 2017) and of astrocyte and oligodendrocyte density (Enache et al., 2019) have been found in the post-mortem brain of depressed individuals, potentially reflecting damages to the blood-brain barrier in this population.

The possibility that the inflammatory activation seen in depression could stem from a pro-inflammatory intestinal environment, facilitated by a compromised intestinal barrier, has also been supported by animal studies. Rodent models of depression are using naturalistic stressors of psychosocial nature (e.g., chronic social defeat) or regimens of variable stressors administered according to a chronic and/or unpredictable sequence (e.g., chronic mild stress) (Golden et al., 2011; Willner, 2005). These procedures activate a chronic human response that may constitute risk factors for depression (Marin et al., 2011) and have demonstrated immunogenic properties (Hodes et al., 2014; Krishnan et al., 2008). Our work and that of others showed that chronic social stressors in adult male mice disturbed gut microbiota communities (Bailey et al., 2011; Bharwani et al., 2016; McGaughey et al., 2019; Szyszkiwicz et al., 2017; Yang et al., 2017) and increased pro-inflammatory cytokines, particularly IL-6, peripherally and in brain regions involved in stress-related disorders (Audet et al., 2010, 2011; Hodes et al., 2014; Menard et al., 2017). Using chronic social defeat in male mice, we showed that some of the long-lasting bacterial changes in cecum contents were linked to severity of social avoidance (a behavioral feature reflective of susceptibility to the depressive-like effects of the stressor) and to brain pro-inflammatory cytokines (Szyszkiwicz et al., 2017). Although these observations were correlational, considering that the genera affected by the social stressor and correlated to behavioral and brain cytokine phenotypes (Oscillospira and Parabacteroides) have anti-inflammatory properties (Koh et al., 2018; Yang et al., 2019), they suggest that severity of social avoidance in chronically defeated mice could be linked to an increased inflammatory tone along the gut microbiota-immune-brain axis. We confirmed this possibility by showing that male mice exposed to chronic social defeat had long-lasting elevations of the pro-inflammatory cytokines IL-1β and TNF-α in the middle section of the small intestine (jejunum), which were accompanied by abnormal expression of tight junction proteins (reflective of increased membrane permeability) (Santos et al., 2021). These findings further support the possibility that stress-induced pro-inflammatory shifts in the intestinal environment, combined with a breach in the intestinal barrier, could promote extra-intestinal inflammatory activation, potentially ramifying to the brain. Considering that these outcomes have been observed in a mouse model of depression, it is possible to think that they could relate, at least in part, to the inflammatory pathways underlying some forms of the illness, as it has been suggested by others (Doney et al., 2021).

3. Inflammatory pathways mediating the gut-brain crosstalk and their development in stressful conditions

The mechanistic pathways by which gut bacteria and the brain talk to each other are only starting to be uncovered. Although it is acknowledged that inflammatory molecules transit between the gut and the brain to relay key messages, how these routes are being established, and how their trajectories may change under adverse conditions, has yet to be defined. Beyond promoting changes in gut microbiota communities and in inflammation (Audet et al., 2010, 2011; Bailey et al., 2011; Bharwani et al., 2016; Hodes et al., 2014; Menard et al., 2017; Szyszkiwicz et al., 2017), stressors induced damages to the intestinal barrier and allowed the passage of bacterial fragments from the intestinal lumen to the bloodstream in male rodents and in humans (Bailey et al., 2006; Karl et al., 2017; Söderholm et al., 2002). These fragments, referred to as microbial-associated molecular patterns (MAMPs), are recognized by pattern recognition receptors (PRRs) on immune cells, which once activated, promote pro-inflammatory cytokine synthesis and release (Takeuchi and Akira, 2010). The endotoxin LPS is recognized mainly by Toll-like receptor 4 (TLR4), but also by TLR2, whereas peptidoglycan (PGN; cell wall component of Gram-positive and to a lesser extent Gram-negative bacteria) is recognized principally by Nod-like receptor 1 (NOD1), as well as by NOD2, TLR2, and peptidoglycan recognition proteins (PGRPs), particularly PGLYRP2 (Takeuchi and Akira, 2010) (Fig. 1). The pro-inflammatory cytokines produced in response to LPS-TLR4 or PGN-NOD1 binding are identical to the cytokines elevated in individuals with major depression (IL-6, TNF-α, and to a lesser extent IL-1β) or, in some instances, found to promote depressive-like states when administered exogenously (IFN-α) (Richez et al., 2009; Takeuchi and Akira, 2010), supporting a role for these inflammatory signaling pathways in depression.

Increases of LPS in the bloodstream and of TLR4 in the brain have been reported in male rats after exposure to acute and chronic stressors (Gara et al., 2011, 2014) and TLR-4 was up-regulated in post-mortem prefrontal cortex of individuals with major depression (Pandey et al., 2019). A role for LPS derived from the gut microbiota and its downstream signaling upon stressor exposure has been confirmed by the observation that a LPS-inhibiting antibiotic prevented plasma IL-1β and IL-18 (Maslanka et al., 2012) and prefrontal TLR4 (Gara et al., 2011, 2014) elevations ordinarily induced by a stressor in male rats. In support of the view that LPS-TLR4 signaling is involved in abnormal behavioral patterns
behaviors, germ-free rodents had impairments in microglia activity and barrier integrity as well as reduced anxiety- and depressive-like behaviors (Braniste et al., 2014; Diaz Heijtz et al., 2011; Eny et al., 2015; Neufeld et al., 2011; Thion et al., 2018).

Beyond the passage of inflammatory molecules in the bloodstream, the modulation of neural innervation of the vagus nerve or the spinal cord may also contribute to the inflammatory crosstalk between the gastrointestinal tract and the brain (see Cryan et al., 2019 for a detailed review). Gut microbiota-derived neuroactive molecules (e.g., hormones, neurotransmitters) as well as bacterial fragments such as LPS may be detected by receptors located within the enteric nervous system, the dorsal root ganglia, and the vagus nerve (Barajon et al., 2009; Egerod et al., 2018; Hyland and Cryan, 2016). In support of a role for gut-brain neural inflammatory signaling in host brain function and behavior, vagotomy reduced microglia activation in the rat hippocampus (Ronchi et al., 2012) and limited the depressive-like phenotype, plasma cytokine elevations, and gut microbiota alterations promoted by LPS in male mice (J. Zhang et al., 2020).

4. Microbiota-targeted interventions for mental health improvements

The effects of dietary patterns on the gut microbiota are now well recognized (David et al., 2014; Sandhu et al., 2017). Although the exact mechanisms by which diet modulates brain function and influences mental health are not entirely elucidated, they point to the involvement of pathways related to inflammation, oxidative stress, mitochondrial dysfunction, tryptophan-kyurenine metabolism, and neurogenesis, to name a few (Marx et al., 2021). A study in male mice has also shown that a diet enriched in prebiotics decreased microglial activation and reduced anxiety-like behaviors (Boehme et al., 2019), suggesting that targeting the gut microbiota using dietary interventions may possibly influence brain inflammatory activity, with potential impact on behavior.

The emerging field of Nutritional Psychiatry has seen a rapidly growing number of observational and experimental studies in the past decade, supporting a role for healthy dietary patterns and dietary interventions in improving mental health (Berding et al., 2021; Marx et al., 2021). Although targeting gut microbes using dietary supplementation has shown mitigated efficacy in improving depressive symptoms (Firth et al., 2019; Goh et al., 2019; Scheff et al., 2017), the use of whole-diet approaches appears promising in reducing symptoms of mental illnesses (Berding et al., 2021). Adherence to dietary patterns based on the Mediterranean diet, characterized by high intakes of fruits, vegetables, whole grains, legumes, fish, nuts, and extra virgin olive oil, has consistently been associated with low risk for depression, anxiety, and psychological distress (Akbaraly et al., 2009; Li et al., 2017; Sadeghi et al., 2019). Notably, the efficacy of Mediterranean-based diet interventions in improving symptoms in patients with depression has been confirmed in a few studies, highlighting the therapeutic prospects of the diet for this illness (Jacka et al., 2017). The mechanisms behind the mood-improving effects of the Mediterranean diet have yet to be entirely defined, although it has been shown to increase levels of the beneficial bacteria Faecalibacterium prausnitzii and Bacteroidetes as well as those of the short-chain fatty acids propionate and butyrate (Gutierrez-Diaz et al., 2016; Meslier et al., 2020).

5. Conclusion and future directions

Major depression is the leading cause of disabilities worldwide and only 30% of individuals with the illness completely remit after their first treatment (Trivedi et al., 2006), suggesting that first-line antidepressants may not be targeting all the biological systems at play in this heterogeneous illness and that alternative and/or complementary therapeutic approaches could alleviate symptoms. Although there is no unanimity on what a “mentally healthy” or a “mentally ill” gut microbiota is (Dinan and Cryan, 2017), appreciable evidence points to the presence of
pro-inflammatory shifts in gut microbiota communities in individuals with depression (Chen et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Valles-Colomer et al., 2019; Zheng et al., 2016). As suggested here and by others (Doney et al., 2021), the possibility exists that pro-inflammatory changes in the gut microbiota, as seen under chronic stress, could play a role in promoting brain inflammatory activity in depression, by transitioning from the gut environment to circulation and to the brain through impaired gut and blood-brain barriers. Although data in this regard are still limited, consistent findings are supporting whole-diet interventions focusing on the intake of plant-based foods with a high content of grains/fibers, fermented foods, polyphenols or polyunsaturated fatty acids in the context of depression (Dinan et al., 2019). The development of such approaches, focused on targeting beneficial intestinal microbes, may have the potential to help dampening the inflammatory effects of stressors on the gut microbiota-immune-brain axis in vulnerable populations and improve mental health when used as alternative and/or complementary approaches to prevent and/or alleviate symptoms. Finally, as it has been previously emphasized (Audet et al., 2019), there is a pressing need for animal- and human-based research to be conducted in males and females to better characterize sex differences in relation to inflammatory-related depression and thus better inform the development of evidence-based interventions for this illness.

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Declarations of competing interest
None.

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