The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota?

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ABSTRACT

Accumulating evidence indicates that patients with severe mental disorders, including major depression, bipolar disorder and schizophrenia present with various alterations of the gut microbiota and increased intestinal permeability. In addition, the hypothalamic-pituitary-adrenal (HPA) axis dysregulation and subclinical inflammation have been reported in this group of patients. Although it has been found that the HPA axis dysregulation appears as a consequence of psychosocial stress, especially traumatic life events, the exact mechanisms of this observation remain unclear. Animal model studies have unraveled several mechanisms linking the gut microbiota with the HPA axis dysfunction. Indeed, the gut microbiota can activate the HPA axis through several mediators that cross the blood-brain barrier and include microbial antigens, cytokines and prostaglandins. There is also evidence that various microbial species can affect ileal corticosterone production that may impact the activity of the HPA axis. However, some metabolites released by various microbes, e.g., short-chain fatty acids, can attenuate the HPA axis response. Moreover, several bacteria release neurotransmitters that can directly interact with vagal afferents. It has been postulated that the HPA axis activation can impact the gut microbiota and intestinal permeability. In this article, we discuss various mechanisms linking the gut microbiota with the HPA axis activity and summarize current evidence for a cross-talk between the gut-brain axis and the HPA axis from studies of patients with mood and psychotic disorders. Finally, we show potential clinical implications that can arise from future studies investigating the HPA axis activity with respect to the gut microbiota in severe mental disorders.

1. Introduction

Severe mental disorders, including major depression, bipolar disorder and schizophrenia are ranked among most substantial causes of disability worldwide (Vigo et al., 2016). They represent complex phenotypes with multidimensional psychopathology and overlapping diagnostic boundaries (Misiak et al., 2016). The pathophysiology of severe mental illness remains largely unknown; however, both mood and psychotic disorders share similar risk factors. For instance, convincing evidence indicates that stressful experiences play an important role in the etiology and progression of severe mental illness. It has been shown that a history of childhood trauma increases a risk of mood and psychotic disorders, and may be associated with unfavorable clinical and functional outcomes in this group of patients (Jaworska-Andryszewska and Rybakowski, 2019; Misiak et al., 2017). However, it is important to note that early-life stress is not specific to any of these disorders and may contribute to a broad range of psychopathological manifestations. Moreover, there is still a considerable number of patients with mood and psychotic disorders who do not report a history of childhood adversities (Bonoldi et al., 2013; Marangoni et al., 2016; Rafiq et al., 2018). According to the neural-diathesis model of schizophrenia, childhood adversities act on a pre-existing vulnerability that originates from various early-life insults, including, i.e., genetic liability (Walker and Diforio, 1997). Apart from early-life stress that likely acts...
on critical periods of the brain development, psychosocial stressors occurring in later life may also impact a risk of mood and psychotic disorders or they may trigger illness relapse (Braniste et al., 2014; Spadoni et al., 2015).

In general, stress can be defined as the state of disturbed homeostasis that occurs in case of a real or perceived threat. Stress is an inherent part of the human life and thus various mechanisms have been developed to restore homeostasis. Exposure to stress primarily leads to the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system that enable adaptation to environmental demands. However, overactivation of these mechanisms, in case of chronic stress, traumatic experiences or ineffective coping, might trigger systemic biological responses that exert deleterious effects. Various biological dysregulations that occur in the course of psychotic and mood disorders can be attributed to stress exposure, including the HPA axis dysfunction, subclinical inflammation, low levels of brain-derived neurotrophic factor (BDNF), epigenetic dysregulation and metabolic disturbances (Aas et al., 2019; Baumeister et al., 2016; Misiak et al., 2015; Theileritis et al., 2014). The HPA axis activation represents one of primary responses to stressful stimuli. On the other hand, there is evidence that stress exposure may affect the gastrointestinal barrier, increasing the gut permeability and inducing autoimmunity. The integrity of the blood-brain barrier (BBB) depends on intestinal microbiota (Braniste et al., 2014; Spadoni et al., 2015), and microbiota alterations can be associated with the BBB impairment (Geng et al., 2020). However, the associations between the gut microbiota alterations, intestinal permeability and behavioral changes are not clear. Kuti et al. (2019) found that early-life stressful events and adult chronic stress in mice result in alterations of the gut microbiota and dysfunction of gut barrier along with increased locomotor activity, anxiety-like behavior and nephophia. In this study, rifaximin treatment resulted in a decrease of stress-induced microbial alterations. However, stress-induced behavioral alterations remained unaltered.

In addition, various stressors, including maternal separation, social defeat, physical restraint, noise and crowding can impact the gut microbial composition, leading to microbial alterations in animal models (Cussotto et al., 2018). Over forty years ago, Tannock and Savage (1974) revealed that changing the environment of mice by moving them into the cage without bedding, food and water decreases the number of Lactobacilli. Similarly, a social disruption stressor has been found to decrease the relative abundance of Bacteroides, and increase the relative abundance of the Clostridium genus (Bailey et al., 2011).

It is of great importance that the HPA axis dysregulation can be observed in patients at various stages of mood and psychotic disorders. However, the exact mechanisms underlying this observation remain unknown. There are studies showing that the HPA axis activity is associated with the gut microbiota composition. Therefore, in this article we provide a summary of potential mechanisms linking stress exposure, the gut microbiota and the HPA axis with relevance to severe mental disorders, including major depression, bipolar disorder and schizophrenia.

2. A cross-talk between the gut-brain axis and the HPA axis

2.1. The gut-brain axis – a brief overview

The gastrointestinal tract contains trillions of various microorganisms that include bacteria, fungi, archaea and viruses (Guarnieri and Malagelada, 2003). The human adult gut is the home for 10^{14} bacteria and equals the number of somatic cells in the human body (Sender et al., 2016). The gut microbiota is mainly represented by bacteria that belong to 500–1000 different species. In the physiological state, the gut microbiota in adults are mainly composed by two phyla – Firmicutes and Bacteroidetes (over 90% of intestinal microorganisms) (Jandhyala et al., 2015). However, it has been shown that the gut microbiota composition for every individual is unique and harbors many specific functions related to the host nutrient metabolism, maintenance of structural integrity of the mucosal barrier, immunomodulation, and protection against pathogens (Rinninella et al., 2019). The gut microbes are subjected to dynamic changes throughout the lifespan. There is evidence that microorganisms start to colonize the gastrointestinal tract as early as the fetus begins to swallow the amniotic fluid, i.e., 10 weeks after conception (Golofast and Vales, 2020). Indeed, certain bacterial cultures can be found in the amniotic fluid (DiGiulio, 2012; DiGiulio et al., 2008; Jiménez et al., 2005), placenta (Collado et al., 2016) and the meconium from healthy newborns (Jiménez et al., 2008). During the first years of life, the gut microbiota is subjected to dynamic changes and reaches stability at the age of 3 years, resembling the adult microbial composition (Voreades et al., 2014).

Intestinal microbes serve as primary components of the gut-brain axis that includes various pathways enabling communication between the gut and the central nervous system. These pathways include the communication through various parts of the nervous system and the bloodstream (Skonieczna-Zydecka et al., 2018a, 2018b). The intestine consists of the enteric nervous system (ENS) that is able to act independently of the brain and the spinal cord (Furness, 2012). It has been estimated that about 500 million neurons build up the ENS, and due to its independence, it is perceived as the “second brain”. However, the ENS can interact with the autonomic nervous system via the vagus nerve and prevertebral ganglia. Other pathways are related to gut hormones, the immune system, the HPA axis, tryptophan metabolism and various metabolites released by microbial species, e.g. short-chain fatty acids (SCFAs). Interestingly, the ENS is not the only example of “the gut autonomy”. Indeed, it has been demonstrated that the ileum can also produce corticosterone. The pattern of ileal corticosterone production is cophasic with the adrenal production of corticosterone (Mukherji et al., 2013). However, adrenalectomy does not affect the ileal corticosterone synthesis (Noti et al., 2010). Importantly, a lack of microbiota results in a permanent overproduction of corticosterone by the ileum (Mukherji et al., 2013). This overproduction may contribute to systemic deleterious effects, such as hypercortisolism, hyperglycemia, insulin resistance and dyslipidemia (Vegiopoulos and Herzig, 2007).

2.2. The HPA axis

The HPA axis is one of the most important components of the gut-brain axis and provides primary biological response to stressful stimuli. The activity of the HPA axis is initiated in the hypothalamus by the synthesis of the corticotrophin-releasing hormone (CRH) by the paraventricular nucleus. This hormone stimulates the production of the adrenocorticotropic hormone (ACTH) in the pituitary gland. In addition, CRH activates locus coeruleus, thereby increasing noradrenergic activity in the brain (Jedema and Grace, 2004). In turn, ACTH leads to the release of glucocorticoids from the adrenal cortex. Hormones of the HPA axis act in a negative feedback loop, i.e., cortisol reduces its own secretion by signaling a feedback to the hypothalamus and the pituitary gland to decrease the production of CRH and ACTH. Notably, the paraventricular nucleus is regulated by various neural circuits of the autonomic nervous system and the limbic system (Smith and Vale, 2006). Cortisol, representing glucocorticoids, enhances gluconeogenesis, suppresses immune response as well as increases fat and protein metabolism. Its secretion is subjected to circadian regulation with the highest levels in the early morning and the lowest production at midnight. Increased secretion in the early morning is called the cortisol awakening response (CAR). This circadian pattern develops during the first six months of life, and there is evidence that intestinal microbiota develops in parallel with the HPA axis (de Weerth, 2017).
2.3. Insights into the association between the gut-brain axis and the HPA axis

Several experimental studies suggest the association between the gut microbiota and the HPA axis. As mentioned above, various stressors might impact the abundance of Lactobacillus, Bacteroides and Clostridium in animal models as well as intestinal integrity (Bailey and Coe, 1999). This effect might appear through direct effects of catecholamines released in response to stress, which can stimulate the growth of the Gram-negative bacteria (Lyte and Ernst, 1992). Moreover, probiotics based on Lactobacillus and Bifidobacterium have been found to restore stress-induced HPA axis dysfunction and improve learning, memory as well as depression- and anxiety-like symptoms (Desbonnet et al., 2010; Eutamene et al., 2007; Gareau et al., 2007). Germ-free mice have also been found to present with the indices of the HPA axis hyperactivity in response to stress (Clarke et al., 2014; Crumeyrolle-Arias et al., 2014; Sudo et al., 2004b). It has recently been shown that these alterations are not limited to blood markers. Indeed, it has been reported that genes involved in the HPA axis response are up-regulated in the hippocampus of germ-free mice (Luo et al., 2018). Interestingly, in the study by Sudo et al. (2004a, 2004b), enhanced HPA axis response in germ-free mice was reversed by the reconstitution with Bifidobacterium infantis (Sudo et al., 2004a). Similarly, probiotic treatment has been shown to lead to attenuated HPA axis response to an acute psychological stress in rats (Ait-Belgnaoui et al., 2012) and might prevent abnormal brain activity related to chronic stress in mice (Ait-Belgnaoui et al., 2014).

Findings from human studies further support these observations. Hantsoo et al. (2019) found that pregnant women with a history of childhood adversities have greater differential abundance of Prevotella (Hantsoo et al., 2019). Moreover, the abundance of several taxa in this study was associated with cortisol levels. A double-blind, placebo-controlled, randomized trial of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 demonstrated their beneficial effects on the level of perceived stress in a non-clinical sample (Messaoudi et al., 2019). Interestingly, in the study by Sudo et al. (2004a), enhanced HPA axis response in germ-free mice was reversed by the reconstitution with Bifidobacterium infantis (Sudo et al., 2004a). Additionally, probiotic treatment has been shown to lead to attenuated HPA axis response to an acute psychological stress in rats (Ait-Belgnaoui et al., 2012) and might prevent abnormal brain activity related to chronic stress in mice (Ait-Belgnaoui et al., 2014).

To date, various mechanisms have been proposed to explain the association between the gut microbiota and the HPA axis (summarized in Fig. 1). First, the gut microbial alterations (dysbiosis) may contribute to enhanced release of cytokines and synthesis of small bioactive molecules. In turn, certain cytokines, including interleukin(IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) might pass through the BBB and be potent activators of the HPA axis (Banks, 2005; Turnbull and Rivier, 1995). Second, the HPA axis can also be activated by the release of lipopolysaccharide (LPS) (Vakharia and Hinson, 2005) and peptidoglycan (the cell wall component of most bacteria) (Arentsen et al., 2017). Third, E. coli can produce the ClpP protein that mimics α-melanotrophin (α-MSH) (Breton et al., 2016). In turn, α-MSH can stimulate the release of proopiomelanocortin that is a substrate for ACTH synthesis. At this point, a particular attention should be paid to SCFAs that are produced during fermentation of indigestible carbohydrates by bacteria. They are represented by acetate, butyric acid and propionic acid. Notably, SCFAs exert several beneficial effects for the intestinal environment by stabilizing the gut integrity and down-regulating immune-inflammatory processes (Farzi et al., 2018). Moreover, SCFAs are able to cross BBB and decrease the activity of microglia, limiting local inflammatory processes. It has also been shown that SCFAs can decrease the expression of genes encoding proteins involved in the HPA axis (van de Wouw et al., 2018). Last but not least, the host-microbe interactions can affect the pool of intestinal and bone marrow stem/progenitor cells, influencing their self-renewal, differentiation and regenerative potential on the ENS and the central nervous system (Marlicz et al., 2019). Another important way of communication between the gut microbiota, the central nervous system and the HPA axis is related to direct interactions with the ENS and the vagus nerve (Parashar and Udayabanu, 2016). At this point, it is important to note that several microorganisms can produce neurotransmitters, such as acetylcholine (Lactobacillus plantarum), dopamine (e.g., Bacillus, Proteus vulgaris, Serratia marcescens), GABA (Lactobacillus and Bifidobacterium), histamine (e.g., Citrobacter, and Enterobacter), noradrenephrine (Bacillus, E. coli and Saccharomyces) and serotonin (e.g., Candida, E. coli, Enterococcus and Streptococcus) (Strandwitz, 2018). Microorganisms may also play a role in the transport of catecholamines (Singh et al., 2007). Furthermore, intestinal microbiota can affect tryptophan availability (Racker et al., 2018). These observations are of great importance since the nucleus of the solitary tract receives inputs from the sub-diaphragmatic vagus nerve (Paton et al., 1999). This nucleus activates the HPA axis through noradrenergic neurons (Herman et al., 2016). It cannot be ruled out that the association between the gut microbiota and the HPA axis also follows an opposite direction. Indeed, there is evidence that abnormal solicitation of the HPA axis during the brain development can impact microbial colonization and visceral sensitivity (Pellissier and Bonaz, 2017). This direction of causality has been proposed based on studies on irritable bowel syndrome. According to studies in this field, cortisol can directly activate resident immune cells and extrinsic primary afferents in the gastrointestinal tract (Moloney et al., 2016). Notably, it has been demonstrated that the prevalence of irritable bowel syndrome is significantly higher in patients with mood and psychotic disorders compared to the general population (Gupta et al., 1997; Lee et al., 2015). Finally, there is evidence from animal model studies that stress-related HPA axis response may increase the gut permeability. Indeed, crowding stress has been found to increase colonic expression of the receptors for the corticotropic-releasing factor (CRF) type 1 in rats (Vicario et al., 2012). Exposure to water avoidance stress has been shown to exacerbate small bowel injury and gut permeability induced by non-steroidal anti-inflammatory drugs in mice. However, administration of meliprastone can attenuate this effect (Yoshikawa et al., 2017). The association between the HPA axis activation and the gut permeability has also been demonstrated in humans. Vanuytsel et al. (2014) revealed that the effect of public speech stressor on gut permeability appears only in men who present with increased cortisol levels.

2.4. A cross-talk between the gut-brain axis in frame of the allostatic load concept

The term “allostasis” was coined to conceptualize physiological responses that enable adaptation to environmental demands driven by stressful situations (McEwen and Stellar, 1993). Mediators of allostasis include various hormones, neurotransmitters, neurotrophins, oxidative stress markers, and immune-inflammatory signals. Short-term activation of these mechanisms might be beneficial in terms of restoring biological homeostasis (“stability through change”) (McEwen and Wingfield, 2003). However, chronic activation of these processes is
unfavorable mental and physical health outcomes have been detrimental and has been termed as the allostatic load (AL). In turn, unfavorable mental and physical health outcomes have been defined as the allostatic overload. This paradigm has provided the basis for developing the AL index that captures a variety of biological dysregulations that correlate with morbidity and mortality (Misiak et al., 2014). To date, various approaches to calculate the AL index have been developed and used in epidemiological studies (Misiak, 2020) and psychotic disorders (Misiak, 2020). It has been proposed that the gut microbiota alterations might represent consequences of the AL (Shiels et al., 2019; Westfall et al., 2019). Emerging evidence also indicates an opposite association, i.e., the AL index activation can contribute to the gut dysbiosis and altered permeability (4). Abbreviations: ACTH - adrenocorticotropic hormone; ClpB - caseinolytic peptidase B; IL-1 - interleukin-1; IL-6 - interleukin-6, LPS - lipopolysaccharide; SCFAs - short-chain fatty acids; TFN-α - tumor necrosis factor-α.

3. The HPA axis dysfunction with respect to gut microbiota in severe mental illness

To date, some animal model and human studies of severe mental illness have provided insights into the association between the gut microbiota and the HPA axis. Subsequent sections summarize most important findings on the HPA axis dysregulation and the gut microbiota alterations in major depression, bipolar disorder and schizophrenia. Moreover, specific correlations between the markers of the HPA axis activity and the gut microbiota are provided.

3.1. Major depression

Main HPA axis abnormalities in major depression include increased secretion and reactivity of cortisol, elevated basal levels of CRH in the cerebrospinal fluid as well as increased volumes and activity of the pituitary and adrenal gland (Zunszain et al., 2011). Moreover, it has been observed that patients with major depression present with glucocorticoid resistance, i.e., elevated cortisol levels are resistant to the feedback regulation by the HPA axis (Pariante, 2017). This phenomenon is at least partially related to a dysfunction of glucocorticoid receptors in this group of patients. However, it is also likely that glucocorticoid resistance develops as the consequence of subclinical inflammation (Perrin et al., 2019). Although subclinical inflammation and glucocorticoid resistance do not occur in all patients with depression, these phenomena may mark treatment-resistance or at least worse response to antidepressants (Carvalho et al., 2013). Apart from treatment-resistant patients, subclinical inflammation appears in patients with a history of childhood trauma (Danese et al., 2008). Available evidence indicates that the association between early-life stress and inflammation falls beyond major depression and serves as a more general phenomenon (Baumeister et al., 2016).

To date, several studies have investigated the association between the gut microbiota and major depression. Cheung et al. (2019) performed a systematic review of six studies comparing the gut microbiota in patients with major depression and healthy controls that analyzed Bacteroidetes, Firmicutes, Actinobacteria, Fusobacteria, and Proteobacteria. They found that nine genera had higher abundance (Anaerostipes, Blautia, Clostridium, Klebsiella, Lachnospiraceae incertae sedis, Parabacteroides, Parasutterella, Phascolarctobacterium, and Streptococcus), six genera had lower (Bifidobacterium, Dialister, Escherichia/Shigella, Faecalibacterium, and Ruminococcus), and six genera were more divergent (Alistipes, Bacteroides, Megamonas, Oscillibacter, Prevotella, and Roseburia) in patients with depression. A recent meta-analysis of 34 controlled clinical trials revealed that probiotics, but not prebiotics, exert small but significant antidepressant and anxiolytic effects (Liu et al., 2019). The anti-depressant effect increased from medium to large in the subgroup analysis of psychiatric samples.

Less is known about the association between gut microbiota and the HPA axis in depression, and available evidence is based on animal
model studies. In one of previous studies in this field, transplantation of the gut microbiota from patients with depression to germ-free mice was associated with the development of anxiety- and depression-like phenotype that was accompanied by a down-regulation of the Stat5a gene in the hippocampus (Luo et al., 2018). Notably, the Stat5a gene is involved in regulating the HPA axis response. It has been found that the treatment with probiotics reduces depressive-like symptoms in the forced swim test in rats and leads to a decrease in the hippocampal levels of transcripts involved in the HPA axis regulation (Abildgaard et al., 2017). Moreover, in a mouse model of maternal separation, administration of Bifidobacterium pseudocatenulatum CECT7765 reduced corticosterone production at baseline and in response to subsequent acute stress in the adulthood (Moya-Pérez et al., 2017). Beneficial effects of this strain on neuroendoctrine functions have also been found in obese mice with anhedonia (Agusti et al., 2018). However, there is a scarcity of human studies addressing a cross-talk between the HPA axis and the gut microbiota in major depression. A recent study demonstrated that administration of Lactobacillus plantarum 299v in patients with major depression improves cognitive performance in terms of attention and verbal learning as well as leads to beneficial changes in the kynurenine pathway. However, no significant changes were observed with respect to cortisol levels (Rudzki et al., 2019).

### 3.2. Bipolar disorder

Evidence from recent meta-analyses indicates that patients with bipolar disorder present with increased levels of cortisol (morning and post-dexamethasone) and ACTH, but not CRH (Belvederi Murri et al., 2016; Girshkin et al., 2014). One of these meta-analyses revealed that higher cortisol levels are positively associated with manic phase and negatively correlated with the use of antipsychotics (Belvederi Murri et al., 2016). There is also evidence that these alterations appear in the offspring of bipolar disorder patients and are associated with a history of childhood trauma as well as a dysfunctional parenting style (Ellenhoren and Hodgins, 2009; Schreuder et al., 2016; Watson et al., 2007). As similar to major depression, these alterations also co-exist with aberrant immune-inflammatory processes (Rosenblat and McIntyre, 2017).

To date, four studies (Aizawa et al., 2016; Coello et al., 2019; Evans et al., 2017; Painold et al., 2019) investigated the gut microbiota in patients with bipolar disorder (for a systematic review see (Vindegaaard et al., 2020)). Findings from one of these studies implies that patients with bipolar disorder, compared to controls, show higher abundance of Actinobacteria (at the phylum level), Coriobacteria (at the class level) and Coriobacteriaceae (at the family level) as well as lower abundance of Faecalibacterium (at the phylum level) and Ruminococcaceae (at the family level) (Evans et al., 2017; Painold et al., 2019). In one of these studies (Coello et al., 2019), Flavonifractor was significantly more prevalent in patients with bipolar disorder, but not in their unaffected first-degree relatives, compared to healthy controls. However, this difference was limited to patients who were cigarette smokers. Although no significant differences in the abundance of specific microorganisms between patients and controls were found in the study by Aizawa et al. (2016), the authors provided some insight into the association between the gut microbiota and the HPA axis. Indeed, a significant negative correlation between the count of Bifidobacterium and cortisol levels was found.

### 3.3. Schizophrenia

The association between the HPA axis dysfunction and schizophrenia is more complex than the one reported in mood disorders. Pituitary enlargement has been reported in subjects at risk of psychosis and seems to be more pronounced in those who develop psychosis; however, this observation is not consistent in patients with first-episode psychosis (Nordholm et al., 2013; Saunders et al., 2019). Increased morning cortisol levels in patients with schizophrenia have been demonstrated in one of previous meta-analyses (Girshkin et al., 2014). The authors also found that this association is more pronounced in patients with schizophrenia compared to those with first-episode psychosis. On the other hand, blunted CAR and cortisol response to stress in patients with schizophrenia and/or first-episode psychosis have been found in other meta-analyses (Berger et al., 2016; Ciufolini et al., 2014; Zorn et al., 2017). Moreover, patients with schizophrenia, at various stages of illness, present systemic biological dysregulations associated with stress that have been conceptualized as increased allostatic load index (Misiak, 2020; Piotrowski et al., 2019). To date, no studies have examined the association between the HPA axis response and the gut microbiota in patients with schizophrenia. The rationale for studies addressing this relationship is not only supported by pre-clinical studies mentioned above but also by the observations from studies investigating the gut microbiota (Pelka-Wysiecka et al., 2019; Skonieczna-Zydecka et al., 2019) and permeability (Rudzki and Szulc, 2018) in this group of patients.

Two studies investigating the gut microbiota in patients with schizophrenia and healthy controls have been published so far. Lower abundance of Firmicutes has been demonstrated in patients with schizophrenia (Shen et al., 2018). However, contradictory findings have been reported for the Proteobacteria phylum (Nguyen et al., 2018; Shen et al., 2018). Studies of patients with first-psychosis have also provided inconsistent results. Yuan et al. (2018) found that drug-naïve patients with first-episode psychosis have a lower number of Bifidobacterium spp., E. coli and Lactobacillus spp. as compared to healthy controls. Another study revealed an increased number of the Lactobacillus group bacteria in patients with first-episode psychosis in comparison with controls. Moreover, a higher number of the Lactobacillus bacteria was associated with higher severity of positive symptoms and worse general functioning (Schwarz et al., 2018).

More studies have investigated the gut permeability and microbial translocation in patients with schizophrenia or FEP. Severance et al. (2012) investigated the levels of antibodies to Saccharomyces cerevisiae (ASCA) that are a diagnostic marker of Crohn’s disease. They found elevated ASCA levels in recent onset and non-recent onset schizophrenia patients compared to controls, and in unmedicated first-episode cases compared to medicated patients. The levels of ASCA were significantly associated with the levels of food antigen antibodies. The same group also examined the levels of soluble CD14 (sCD14) antigens and lipopolysaccharide (LPS) binding protein (LBP) in schizophrenia patients (Severance et al., 2013). Seropositivity of sCD14 conferred over threefold increased odds of association with schizophrenia compared to controls. Both sCD14 and LBP were positively associated with CRP levels, but only the levels of LBP were significantly correlated with the body-mass index. In this study, the levels of sCD14 and LBP were not associated with antipsychotic treatment. Another study investigated the levels of antibodies to Candida albicans in schizophrenia (Severance et al., 2016). Candidal species are the most widely represented commensal fungus in the humans. Candida albicans seropositivity conferred increased odds for a diagnosis of schizophrenia only in males. In female schizophrenia patients, Candida albicans seropositivity was associated with higher odds of cognitive impairment.

It is important to note that antipsychotics may affect the gut microbiota in patients with schizophrenia. First-generation antipsychotics exert anti-inflammatory effects, especially with respect to Gram-positive bacteria (Dinan and Cryan, 2018). In turn, the effect of second-generation antipsychotics, especially olanzapine, on weight-gain has been associated with an increase in the number of Firmicutes and a decrease in the number of Bacteroidetes (Skonieczna-Zydecka et al., 2019). Interestingly, the impact of olanzapine on body weight is not significant in germ-free rodents, suggesting that this adverse treatment effect is mediated by the gut microbiota (Dinan and Cryan, 2018). In parallel, there is evidence that antipsychotics may impact the HPA axis (Handley et al., 2016). Moreover, the use of anti-glucocorticoid medications may
be beneficial in patients with schizophrenia; however, this observation requires additional randomized controlled trials (Garner et al., 2016). A recent systematic review investigating the effect of probiotic supplementation on the improvement of schizophrenia symptoms did not confirm the efficacy of probiotics in the treatment of schizophrenia patients (Ng et al., 2019).

4. Summary of evidence and future directions

There is a growing body of evidence for the involvement of the gut microbiota in the regulation of emotions, behavior, and higher cognitive functions through the ‘microbiome-gut-brain axis’ (Ng et al., 2019). The relationship between the central nervous system and the gut microbiota is pivotal for the neurodevelopment as well as for various brain functions in the adulthood (de Weerth, 2017; Frankienstztn et al., 2020). The connection between the gut microbiota and the brain is bidirectional, and includes endocrine, neural, immune and metabolic pathways (Sun et al., 2019). In this review, we focused on the interactions between the gut microbiota and the HPA axis in the development and symptomatology of severe mental illness. Approaching the host-microbiome interactions from a microbial endocrinology-based point may improve our understanding of the specific pathways by which microorganisms may influence stress-related mental health outcomes.

The HPA axis dysregulation is widely observed in patients with severe mental illness and it is likely that it occurs as a consequence of exposure to various stressors. However, there is convincing evidence that the gut microbial alterations and increased intestinal permeability contribute to this observation. Several mechanisms linking the gut microbiota with the HPA axis dysfunction have already been recognized. According to studies based on animal models, exposure to stress leads to the gut dysbiosis that in turn increases the gut permeability. Various microbial antigens released to the bloodstream can pass through the BBB and activate the HPA axis. Moreover, markers of subclinical inflammation (IL-1, IL-6 and TNF-α) that originates from increased microbial translocation can further contribute to the HPA axis activation. It has also been found that autonomic ileal production of corticosterone may impact the HPA axis activity. Another scenario is related to interactions with vagal afferents through synthesis of neurotransmitters by several bacteria. Although these mechanisms seem to be well-documented by animal model studies, less is known about effects of the HPA axis activation on the gut microbiota and permeability. Moreover, it remains unknown as to whether the gut microbiota alterations might be associated with a broad range of stress-related biological dysregulations captured by the AL concept. It is also warranted to investigate how the gut microbiota influences stem cell trafficking and what is the physiological role of recently reported blood microbiome (Marlicz et al., 2019).

Evidence from human studies that supports the existence of a cross-talk between the gut-brain axis and the HPA axis is largely limited (Frankienstztn et al., 2020; Marlicz et al., 2018; Skonieczna-Żydecka et al., 2018a, 2018b). It is of great importance that the HPA axis dysfunction, subclinical inflammation and the gut dysbiosis appear in a certain subgroup of patients with psychotic and mood disorders (Pariante, 2017). It has been suggested that traumatic life events, especially those acting on critical windows of the brain development, serve as a pre-requisite of the HPA axis dysregulation (Aas et al., 2019) and aberrant immune-inflammatory processes (Baumeister et al., 2016). Some studies have also indicated that poor clinical and functional outcomes in patients with severe mental illness are related to early-life stress (Misiak et al., 2017), the HPA axis dysfunction (Mondelli et al., 2015) and subclinical inflammation (Frydecka et al., 2015). It has been suggested that this subgroup of patients would benefit from specific add-on treatment strategies that target the HPA axis dysfunction and aberrant immune-inflammatory processes (Leboyer et al., 2016). The HPA axis is subjected to programming by early-life events and these effects seem to persist until the adulthood (Meiney et al., 1988; Schmidt et al., 2002; Zijlmans et al., 2015). Interestingly, studies on gnotobiotic mice showed that postnatal exposure to the gut microbiota can affect the set point of the HPA axis (Sudo, 2012). In turn, the hyperactivity of the HPA axis is known to predispose individuals to develop various categories of psychopathology (Jurjena et al., 2020). However, it remains unknown as to whether the gut microbiota alterations also characterize this group of patients and how they can impact the HPA axis activity or subclinical inflammation. Addressing this hypothesis by future studies would provide grounds for developing personalized treatment approaches based on the administration of probiotics or prebiotics.

Some genes encoding critical molecules involved in the HPA axis stress response, such as glucocorticoid receptor and CRF, are now known to be susceptible to epigenetic modifications (Buschdorf and Meany, 2016). However, it remains unknown what molecules and processes are involved in the epigenetic regulation associated with the microbiota-induced changes in the HPA axis activity. It has been hypothesized that butyric acid produced by anaerobic bacteria might play this role (Sudo, 2012) since it may impact the levels of brain-derived neurotrophic factor (BDNF) in the cortex (Sudo et al., 2004b). Moreover, systemic injections of butyrate have been reported to induce histone hyperacetylation in the hippocampus and the frontal cortex that is accompanied by antidepressant-like effects and increased levels of BDNF transcripts in the brain (Schroeder et al., 2007). Moreover, it has been shown that microbiota regulates histone modifications in several intestinal immune cells (Gury-BenAri et al., 2016) and program DNA methylation to control intestinal inflammation (Ansari et al., 2020).

Limitations of previous human studies, investigating gut microbiota in mood and psychotic disorders, should also be considered. As suggested by a recent systematic review of studies comparing the gut microbiota between patients with severe mental illness and healthy controls, generalization of findings with respect to specific alterations cannot be made due to a great variability of methods and reporting (Vindegaard et al., 2020). Moreover, a risk of false positives cannot be excluded because of small sample size in previous studies. Given a scarcity of longitudinal studies, caution should also be taken as to the way causal associations are being established. This aspect is of great importance to the association between the gut microbiota and the HPA axis dysregulation in severe mental illness as direction of causality is yet to be established. Residual confounding factors should be controlled accurately in studies on the gut microbiota, and include ethnic differences as well as a variety of environmental exposures (e.g., dietary habits, physical activity, effects of prior and current medications as well as substance use). Moreover, bacterial diversity changes with age and thus some inconsistencies in the results of previous studies may be explained by between-sample differences in age. Finally, a detailed assessment of clinical characteristics, including psychopathological symptoms, cognitive impairments, comorbid physical health impairments and psychosocial functioning is needed.

Declaration of Competing Interest

None to declare.

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