Review

Influence of early life stress on depression: from the perspective of neuroendocrine to the participation of gut microbiota

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ABSTRACT

Depression is the most common mental disorder and has become a heavy burden in modern society. Clinical studies have identified early life stress as one of the high-risk factors for increased susceptibility to depression. Alteration of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress is one of the key risk factors for depression susceptibility related to early life stress. Laboratory animal studies have demonstrated that maternal separation (MS) for extended periods elicits HPA axis changes. These changes persist into adulthood and resemble those present in depressed adult individuals, including hyperactivity of the HPA axis. In addition, there is growing evidence that inflammation plays an important role in depression susceptibility concerned with early life stress. Individuals that have experienced MS have higher levels of pro-inflammatory cytokines and are susceptible to depression. Recently, it has been found that the gut microbiota plays an important role in regulating behavior and is also associated with depression. The translocation of gut microbiota and the change of gut microbiota composition caused by early stress may be a reason. In this review, we discussed the mechanisms by which early life stress contributes to the development of depression in terms of these factors. These studies have facilitated a systematic understanding of the pathogenesis of depression related to early life stress and will provide new ideas for the prevention and treatment of depression.

INTRODUCTION

Clinical studies have found that early life stress is strongly associated with the development of depression in adulthood [1–4]. Individuals that have experienced early life stress have a significantly higher risk of depression, mania, schizophrenia and other psychiatric disorders in adulthood than those have not experienced early life stress [5]. Early life stress is significantly more associated with the onset of depression than recent stressful events with depression [6]. In addition, patients with depression who experienced a stressful event in childhood showed clinical features such as earlier age of onset, more severe depressive symptoms, more prolonged course, recurrent episodes and significantly reduced efficacy of common antidepressants [7]. Basic research has also shown that early environmental stress induces depression in rodents and primates in adulthood [8]. However, the pathways or mechanisms through which stressful events occurring early in life contribute to the onset of depression are not yet entirely clear. Changes in the HPA axis are thought to be key factors in depression susceptibility [9]. For example, MS can produce significant stress. Long-term exposure to stress will lead to the HPA axis hyperactivity in response to stress, which manifests itself in adulthood and persists. In addition, MS increases susceptibility to depression by altering both serotonin and dopamine secretion in relevant areas of the brain. Besides the endocrine system, MS is also closely linked to the immune system. Inflammatory mechanisms are involved in

enhancing the stress response after early life stress and in the development of vulnerability to depression [10, 11]. Not only that, recent studies have found that the altered gut microbiota caused by MS may also play an important role. Alterations in composition have been found in MS models and rat models of depression. Even fecal transplants from Major Depressive Disorder (MDD) patients affected depression-like behavior in recipient animals [12]. As shown in Figure 1, we demonstrated the association between early-life stress and depression from the perspective of neuroendocrinology, immune and gut microbiota.

Neuroendocrine regulation in early life stress-induced depression

In rodents (especially rats), MS has become a common trigger for various psychiatric disorders, especially depression [13–17]. MS may contribute to depression susceptibility in adulthood through alterations of the HPA axis in response to stress [18, 19], alterations in the expression of BDNF in different regions of the central nervous system (CNS) [20], alterations in the expression of serotonin in the CNS [21] and alterations in the expression of dopamine and its receptors [22] (Table 1).

HPA axis

Studies over the past few decades have demonstrated that hyperactivity of the HPA axis is one of the most consistent biological findings in depression [23–27]. Laboratory animal studies have shown that separating neonatal rodents and non-human primates from their mothers for long periods elicits HPA axis changes. Those changes persist into adulthood and resemble those present in depressed adult individuals, including hyperactivity of the HPA axis [28].

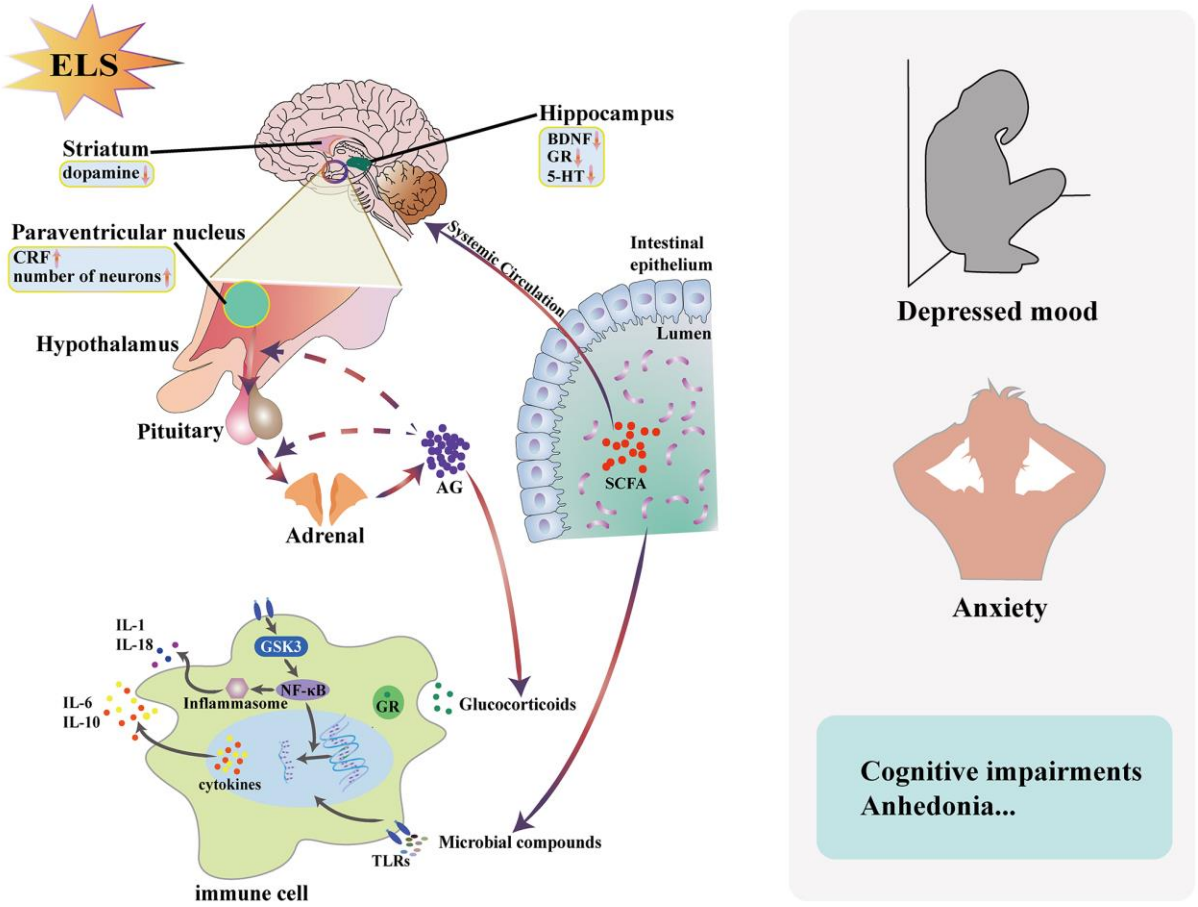

Figure 1. Early life stress (ELS) contributes to the development of depression through the endocrine system, immune system and gut microbiota. ELS can lead to high reactivity of HPA axis response to stress and the disorder of HPA axis is closely related to the development of depression. The imbalance of immune system caused by the disorder of glucocorticoid secretion and the change of gut microbiota are also related to the development of depression. Abbreviations: GR: glucocorticoid receptor; TLR: Toll-like receptor; GRF: corticotropin releasing factor; ELS: early life stress; 5-HT: 5-hydroxytryptamine; IL-1: interleukin-1; IL-6: interleukin-6; IL-10: interleukin-10; IL-18: interleukin-18; BDNF, brain-derived neurotrophic factor; SCFA: short-chain fatty acid; AG: adrenal glucocorticoid; GSK3: Glycogen synthase kinase 3; NF-κB: nuclear factor-κ -gene binding.

Table 1. Neuroendocrine regulation in early life stress-induced depression.

System involved	Stress exposure	Depression-like behavior	Main findings	References
HPA axis	MS	Promoting	Venlafaxine reverses depressive-like behavior induced by MS via modulating HPA axis activity.	Martisova et al., 2015
	MS	Promoting	Acupuncture reverses depressive-like behavior induced by MS via modulating HPA activity.	Park et al., 2011
Serotonin system	MS	Promoting	Serotonergic activity in the hippocampus and the raphe decrease under MS-induced depression.	Jahng, 2011
	MS	Promoting	5-HT synthesis in hippocampal dentate gyrus decreases in the MS rat pups.	Baek et al., 2012
	ELS	Promoting	The ELS-induced decrease of SERT expression relates to altered serotonergic function, and possibly to the susceptibility to depression.	Wankerl et al., 2014
Dopamine system	MS	Promoting	Down regulation of D1 receptors promotes the depression-like behavior caused by MS.	Amiri et al., 2016
Neurotrophins	MS	Promoting	Enriched environment during the early development period is effective in alleviating depression induced by ELS through increasing BDNF expression in the hippocampus.	Huang et al., 2021
	MS	Promoting	Through the BDNF/PKA/CREB pathway, SiNiSan treatment might impose antidepressant effects on young and adult MS rats.	Cao et al., 2019

Abbreviations: MS: maternal separation; HPA axis: Hypothalamic–pituitary–adrenal axis; ELS: early life stress; 5-HT: 5-hydroxytryptamine; CREB: cAMP-response element binding protein; BDNF: brain-derived neurotrophic factor; PKA: protein kinase A.

Male Wistar rats underwent early MS showed significantly reduced glucocorticoid receptor density in the hippocampus in adulthood and exhibited depression-like behaviors in the forced swim test in adulthood [29]. Adult mice also showed lasting consequences of ELS using limited nesting and bedding material paradigm including HPA axis hyperreactivity [30]. Venlafaxine reversed the deleterious effects of chronic stress including stress-induced depression-like behaviors and cognitive deficits. Besides, it reduced subventricular zone volume, demonstrating that modulation of stress-mediated glucocorticoid secretion may be a target for the treatment of mood disorders and neurodegenerative processes [31]. Acupuncture therapies from the East also appeared to improve MS. The HPA axis reactivity was mitigated by acupuncture, specifically by reducing CORT and ACTH plasma levels in MS rats [32]. When endogenous glucocorticoid level is high, GR is more important in regulating HPA axis [33]. In the case of elevated circulating cortisol levels, depressed patients show impaired HPA negative feedback. Many studies have described the decrease of GR function (GR resistance) in patients with depression and concluded that antidepressants play a role by reversing these hypothetical GR changes [34]. When the stress improves over time, depression behavior can be improved to some extent.

Neurotrophins

Not only does MS alter the response of the HPA axis to stress, but MS has also been found to cause alterations in neurotransmitters and brain-derived neurotrophic factor (BDNF) in the brain [35–39], a neurotrophic factor expressed in the brain and associated with neuronal growth, synaptic plasticity, differentiation and neuronal survival [40]. MS decreased hippocampal BDNF and p-AKT/AKT levels and was associated with depression-like behavior, while an enriched environment reversed this negative impact and upregulated the PI3K-AKT pathway [41]. Direct infusion of BDNF into the hippocampus or midbrain yielded antidepressant-like effects [42]. BDNF was also required for the rapid antidepressant effects of ketamine [43]. Some findings indicated that fast transient translation of BDNF was necessary for ketamine's fast-acting and long-lasting antidepressant-like behavioral effects. Those long-term antidepressant responses may be due to alterations in synaptic plasticity initiated by transient increases in BDNF translation [44]. Eukaryotic elongation factor 2 kinase (eEF2K) null knockout mice administered an acute low dose of ketamine did not have increased BDNF protein expression and did not show an antidepressant response to the drug [45].

Serotonin system

In addition to BDNF, serotonin plays an important role in MS-induced depression. Serotonin is closely associated with mood disorders and plays a role in the corticolimbic network that regulates mood, behavior, cognition and motor function. Serotonin transporter gene (SERT) DNA methylation is thought to be related to stress-related diseases. [46, 47]. In mice with MS, 5-hydroxytryptamine (5-HT) synthesis in the dorsal suture nucleus and cell proliferation in the hippocampal dentate gyrus were significantly reduced [48]. Depression-like behavior was also observed in two-month-old MS rats with reduced 5-HT activity in the hippocampus [49]. SERT gene (Solute Carrier Family 6 Member 4, SLC6A4) encodes a protein that transports the neurotransmitter serotonin from the synaptic gap to presynaptic neurons. It has been shown that ELS caused SLC6A4 methylation and that reduced SLC6A4 expression allowed serotonin to accumulate in the synaptic gap [50], thereby impairing normal serotonin function and leading to depression. Besides, MS triggered the decrease in 5-$HT1_A$ receptor expression in the CA1 region in the hippocampus of young and adult male rats compared with control rats without MS, which is also a key factor for depression [20].

Besides 5-HT, a dopaminergic pathway is a part of the reward system. Due to the interaction between the dopaminergic system and HPA axis or the interaction between the dopaminergic system and serotonin system, the effect of chronic stress on reward perception may lead to depression. Some studies have demonstrated that early psychological stress activates the HPA axis, exacerbates DA depletion and is associated with a decrease in DA synthesis in the brain. DA deficiency resulting from early life stress may, in some instances, predispose an individual to depression [51]. In addition, MS causes depression-like behavior in adult male mice with reduced dopamine level in the striatum. A drug that blocks the metabolism of dopamine, selegiline, reduces depression-like behavior in MS mice. Both dopamine receptors D1 and D2 mediate the antidepressant-like effects of selegiline, with D1 receptors mediating the effects on depression behavior and D2 receptors mediating the effects on pleasure deficit [52].

Immunomodulation as a key role in early life stress-induced depression

HPA axis and inflammation modulation under early life stress have a close relationship. Both psychogenic and immune stressors can induce HPA axis and inflammation changes. Maternal care deprivation (a psychological stressor) model increased the levels of pro-inflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)) and decreased the anti-inflammatory cytokine (interleukin-10) level in the brain and serum throughout developmental programming [53]. Meanwhile, early exposure to lipopolysaccharide (an immune stressor) elevated the levels of TNF-α and IL-1β in the hippocampus in adulthood and also increased corticosterone levels in adulthood [54]. There is a growing awareness that people with autoimmune disorders show a high prevalence of depression disorders. By the early 1990 s, the role of overproduction of immunomodulatory signaling molecules for depression became apparent, particularly pro-inflammatory cytokines, which may play a role in the development and maintenance of depression [55]. Interleukin-1 (IL-1), interferon-gamma (IFN-γ), acute-phase associated proteins and tumor cytokines have now been reported to be associated with depression disorder [56]. In addition, treating the hepatitis C virus with pro-inflammatory agents such as interferon-alpha (IFN-α) leads to depression symptoms in a quarter of patients [57]. This inflammatory phenotype is also thought to be an important factor in treatment resistance in depression. This theory led researchers to investigate the antidepressant effects of anti-inflammatory compounds and showed that TNF antagonism improved depressive symptoms in patients with high baseline inflammatory biomarkers [58]. Given that many antidepressants have anti-inflammatory effects [59], immune mechanisms are now thought to be central to the development of depressive symptoms.

Studies have suggested that inflammation plays a key role in early life stress leading to depression susceptibility. Related research results are listed in Table 2. Studies have also showed that repeated MS has pro-inflammatory immune consequences in diverse tissues. Repeated MS animals exhibited greater microglial activation and elevated pro-inflammatory cytokine signaling in key brain regions implicated in human psychiatric disorders. A recent review indicated that minocycline inhibited microglial activation and alleviated depression-like behaviors in male adolescent mice subjected to MS [60]. A prospective study showed that depression adults who experienced severe early life stress were 1.48 times more likely to have clinically high C-reactive protein (CRP) levels than those depression adults without early life stress [61]. In a study that followed adolescent females at higher risk of depression for more than 2.5 years study, adolescents with a history of early life stress had greater increases in IL-6 and CRP when they became depressed than their peers without a history of early life stress. In addition, in this study, adolescents without a history of early life

Table 2. Immunomodulation as a key role in early life stress-induced depression.

Inflammatory cytokine	Stress exposure	Depression-like behavior	Main findings	References
IL-1β	MS	Promoting	IL-1β in the vHIP, PFC and serum increase under ELS-induced depression	Wang et al., 2017
IL-6	MS	Promoting	IL-6 increases under ELS-induced depression.	Miller and Cole, 2012
Il-10	MS	Promoting	IL-10 in the amygdala and hypothalamus decrease under ELS-induced depression.	DellaGioia et al., 2010
TNF-α	MS	Promoting	Pro-inflammatory markers TNF-α is up regulated under ELS-induced depression.	Wang et al., 2017
CRP	ELS	Promoting	CRP increases under ELS-induced depression.	Danese et al., 2008
TLR 4	ELS	Promoting	The expression of gene encoding TLR 4 is up-regulated under ELS-induced depression.	Carroll et al., 2011

Abbreviations: IL-1β: interleukin-1β; MS: maternal separation; vHIP: ventral hippocampus; PFC: prefrontal cortex; IL-6: interleukin-6; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ELS: early life stress; TLR 4: Toll-like receptor.

stress had lower CRP as depressive symptoms decreased. In contrast, adolescents with a history of early life stress did not have this association [62]. There is evidence that the link between early life stress, inflammation and depression is detectable at a young age. A longitudinal study found that patients who experienced early life stress followed by depression had significantly higher CRP level than those who only suffered from depression and did not experience early life stress [63]. Early life stress increased expression of the gene encoding Toll-like receptor (TLR) 4, which activates the innate immune system response. Besides, early life stress reduced the gene expression encoding the glucocorticoid receptor, responsible for down-regulating inflammation in the cortisol response [64]. The above studies have suggested that inflammation plays a vital role in early life stress leading to depression susceptibility.

Studies have shown a sustained process of MS increased inflammatory cytokine secretion in peripheral and brain tissue in mice exposed to lipopolysaccharide (LPS) as adults [65]. Expression of the neuroinflammatory marker Iba1 was increased in MS mice [66]. MS also induced depression-like behavior with microglia activation and over expression of histone demethylase Jumonji domain-containing protein 3 (Jmjd3). These changes can also be found in adulthood. Jmjd3, a trimethylated lysine 27 in histone 3 (H3K27me3) demethylase, can be activated by nuclear factor-kappa B (NF-κB), further regulating the expression of pro-inflammatory cytokines and resulting in neuroinflammation. Treatment with the demethylase Jmjd3 inhibitor GSK-J4 attenuated these changes, suggesting that Jmjd3 is involved in MS-induced depression susceptibility by enhancing neuroinflammation in the rat prefrontal cortex and hippocampus [67]. It has been shown that depression-like behavior following MS stress is associated with increased expression of TLR-4 and its main signaling protein Myd88 in the hippocampus. Voluntary physical activity during adolescence can prevent the negative effect of early life stress. The depression effects of stress are mediated, at least in part, by attenuating the innate immune response in the hippocampus [68]. MS upregulated pro-inflammatory markers TNF-α and downregulated anti-inflammatory markers IL-10 in the hippocampus, which activated microglia and promoted pro-inflammatory shifts in microglia [69]. Early life stress reduced IL-10 expression in the amygdala and hypothalamus [56], and these effects could be reversed by minocycline [70]. Besides, MS increased depression and anxiety behavior with an increased level of IL-1β in the ventral hippocampus (vHIP), prefrontal cortex (PFC) and serum, a decreased level of IL-10 in HPV [69]. Fluvoxamine had similar effects with mRNA levels of IL-1β, IL-6 and TNF-α downregulated in the striatum of fluvoxamine-treated rats. Early treatment with fluvoxamine suppressed depression behavior in MS mice by promoting the expression of anti-inflammatory cytokines [71]. It has been shown that injection of live and heat-killed PS23 cells showed positive behavioral effects in MS animals with increased propensity to explore and activity in behavioral tests and reduced anxiety and depression.

Role of gut microbiota in early life stress-induced depression

Investigation of gut microbiota

In addition to HPA axis and the immune system, gut microbiota shaped by early life stress increased susceptibility to depression in adulthood. The microbiota-gut-brain axis refers to the two-way communication between the gut microbiota and the brain. Although not fully understood, this complex interaction involves multiple physiological systems such as the gastrointestinal system and its gut microbiota, nervous systems, the immune system and the neuroendocrine system [72]. The gut microbiota has emerged as an important brain and behavior regulator linked to depression [73]. Maes et al. suggested that gut microbiota translocation or leaky gut may be a major trigger for the development of depression. Gut microbiota translocation or leaky gut can activate immune cells and stimulate selective immunoglobulin A (IgA) and immunoglobulin M (IgM), which indicating that gut microbiota may be involved in the pathophysiology of depression by causing a progressive immune response [74]. In addition, recent studies have shown that the gut microbiota regulate the maturation of microglia, possibly through the serotonin pathway or the secretion of metabolites such as short-chain fatty acids (SCFA) [75].

Meanwhile, early life stresses, such as maternal immune activation and MS, have been shown to produce gut defects such as increased gut permeability, which lead to translocation of gut microbiota [76]. Therefore, it can be speculated that altered gut permeability and translocation of gut microbiota due to early life stress are closely linked to subsequent depression episodes. Besides, early life stress shaped the gut microbiota and was associated with disease in later adulthood [77, 78]. Chronic exposure to limited nesting stress during the first-week postnatally has sustained effects monitored at weaning including hypercorticosteronemia, a leaky gut and a decreased gut microbiota diversity [79]. However, the underlying mechanisms by which stress regulates microbial community composition remain to be elucidated. For example, a large body of evidence suggested that depression is associated with alterations in the gut microbiota composition, often manifested as a reduction in abundance and diversity, fecal microbiota transplantation is expected to treat diseases related to intestinal gut microbiota disorder. [12, 80]. 16S rRNA analysis of fecal samples from healthy individuals revealed that the most abundant bacteria in terms of numbers were phylum *Aspergillus*, accounting for 70–75% of the entire, with other bacteria also included phylum *Aspergillus*, phylum *Actinomycetes*, phylum *Clostridium* and phylum *Verrucomicrobial* [81]. The proportional number of microbiota differed in depression patients. Compared to healthy people, the largest numbers were found in the phylum *Anaplasma* and lower numbers in the family *Lachnospiraceae* [82]. Similar studies in 2015 found that patients with depression had higher levels of *Bacteroides*, *Proteus* and *Acinetobacter*, while the number of *Firmicutes* was significantly lower [83].

Recently, researchers used DNA sequencing to analyze the microbiota in the feces of more than 1000 people in the Flemish gut microbiota in Belgium found that *Coprococcus* and *Dialisterwere* reduced in patients with depression. There was a positive correlation between their quality of life and the potential ability of the gut microbiota to synthesize 3,4-dihydroxyphenylacetic acid, a breakdown product of the neurotransmitter dopamine [84]. These results were the strongest evidence to date that a person's microbiota can influence their mental health. Analysis of the gut microbiota of MS rats revealed alterations in the composition of their gut microbiota. Member of the *actinomycetes* was reduced, while the abundance of member of the *proteobacteria* was elevated [83].

Therapeutic potential of probiotics

Probiotic interventions have also been shown to reduce depression-like behavior in rats and mice and improve inflammatory responses (Table 3). In addition, some probiotics have now been found to reverse early life stress-induced gut microbiota disturbances and persistent activation of the HPA axis. Eicosapentaenoic acid/Docosahexaenoic (EPA/DHA) acid treatment normalizes the interference of early life stress on gut microbiota in female rats. The altered composition of the gut microbiota resulted in reduced levels of gut permeability and thus reduced inflammation [85]. *Bifidobacterium pseudocatenulatum CECT7765* can also ameliorate MS-induced gut inflammation (decreased interferon-gamma, IFN-γ), which improves depression-like behaviors [86]. As shown in Figure 2, early stress can affect depression through gut microbiota. *Bifidobacterium (B.) bifidum G9-1* prevents MS-induced hypercortisolemia, reduces MS-induced high corticosterone level [87]. Bifidobacterium infantis decreased depression-like behavior in MS mice in forced swimming and sucrose preference test [88]. Mice administered with live *Lactobacillus paracasei PS23 (PS23)* cells had lower serum corticosterone levels and higher serum anti-inflammatory interleukin-10 (IL-10) levels, suggesting that the effect of probiotics may be associated with immunomodulatory properties. Ingestion of *PS128* ameliorated depression-like

Table 3. Role of gut microbiota in early life stress-induced depression.

Probiotics	Stress exposure	Depression-like behavior	Main findings	Reference
Bifidobacterium pseudocatenulatum CECT7765	MS	Promoting	B. pseudocatenulatum CECT 7765 administration reduces depression-like behavior in adulthood, reverses intestinal dysbiosis and reduces corticosterone production.	Moya-Pérez et al., 2017
Bifidobacteria	MS	Promoting	Bifidobacteria treatment results in normalization of immune response and reversal of behavioral deficits.	Fukui et al., 2018
Lactiplantibacillus plantarum PS128	MS	Promoting	Ingestion of PS128 ameliorates depression-like behaviors and modulates neurochemicals.	Liu YW al et al., 2016
Lactobacillus paracasei PS23	MS	Promoting	PS23 cells decrease serum corticosterone levels accompanied by higher serum anti-inflammatory IL-10 levels with reducing depression-like behavior.	Liao et al., 2019
Heat-killed Lactobacillus paracasei PS23	ELS	Promoting	PS23 reverses ELS-induced depression-like behaviors.	Wei et al., 2019

Abbreviations: MS: maternal separation; ELS: early life stress.

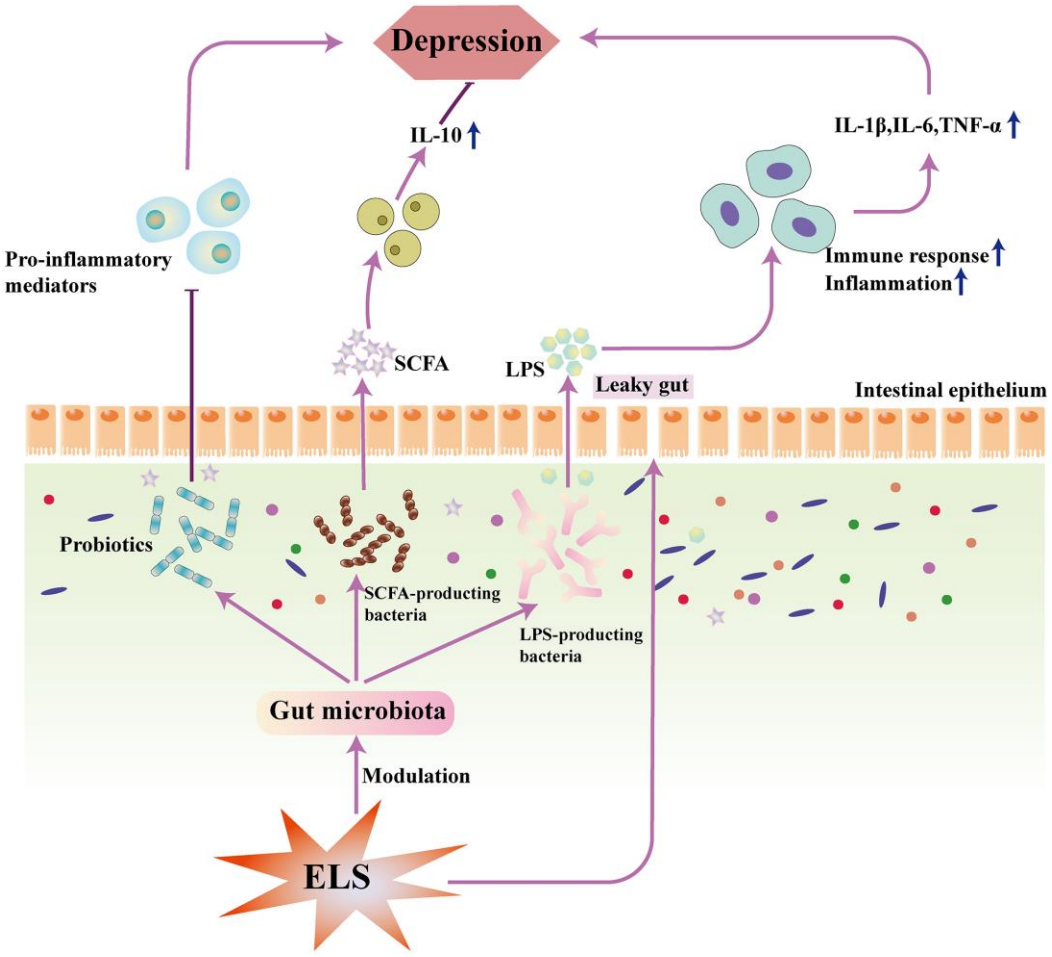

Figure 2. Early life stress produces gut defects and increases gut permeability, leading to translocation of LPS and gut microbiota. LPS can aggravate the body's inflammatory response and increase the risk of depression. Probiotics and SCFA can reverse this process and reduce the risk of depression. Abbreviations: LPS: lipopolysaccharide; SCFA: short-chain fatty acid; ELS: early life stress; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α.

behaviors and modulated neurochemicals related to affective disorders [89]. The study demonstrated the potential of *PS23* cells in reversing abnormalities induced by early life stress [90]. Interestingly, both live and heat-killed *PS23* also reversed anxiety-like and depression-like behaviors induced by chronic corticosterone administration in mice [91].

The current research is mainly based on specific gut microbiota, their metabolites and neurological symptoms. But these correlations do not prove cause and effect. Besides, many studies have used animal models that do not accurately reflect human characteristics or behavior. Studies on humans are relatively few. They are usually based on relatively small populations that may not control for many confounding factors that may affect the gut microbiota, such as abnormal diets, antibiotics or antidepressants. The relationship between early stress and the interaction of gut microbiota and its metabolites deserves to be further studied to find a new therapeutic target to reduce the negative effects of early stress.

CONCLUSIONS

The delicate balance between the stress response, immunity and gut microbiota is crucial for nervous system health. Early life stress can result in the dysregulation of brain physiology and behavior, contributing to the development of depression. More cohort studies are needed to further reveal the effect of early life stress on adulthood. Till now, how to reduce the effect of early life stress on adulthood is also a problem worthy of study. Meanwhile, much work is also needed at a mechanistic level in preclinical and human studies to tease apart the relative contribution of each of them and the cross-talk between each other.

As stated in the introduction, we now appreciate that imbalanced stress and inflammatory responses induced by early life stress are undoubtedly involved in the development and maintenance of depression, but recent evidence suggests that the gut microbiota, too, may play a role in the imbalance of these pathways and neuropsychology. The role of the microbiota in disease is only now emerging, particularly in the field of neuropsychology. Further studies may focus on the cross-talk between the microbiota and neuroendocrine or immune system under early life stress and related intervention therapy.

AUTHOR CONTRIBUTIONS

XT and HX had the idea for the review article. XT drafted the manuscript. HX critically revised the manuscript. LQZ, DNW, SDG, PL and XLX critically reviewed the manuscript for important content. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

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