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The role of enteric nervous system and GDNF in depression: Conversation between the brain and the gut

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ABSTRACT

Depression is a debilitating mental disorder that causes a persistent feeling of sadness and loss of interest. Approximately 280 million individuals worldwide suffer from depression by 2023. Despite the heavy medical and social burden imposed by depression, pathophysiology remains incompletely understood. Emerging evidence indicates various bidirectional interplay enable communication between the gut and brain. These interplays provide a link between intestinal and central nervous system as well as feedback from cortical and sensory centers to enteric activities, which also influences physiology and behavior in depression. This review aims to overview the significant role of the enteric nervous system (ENS) in the pathophysiology of depression and gut-brain axis's contribution to depressive disorders. Additionally, we explore the alterations in enteric glia cells (EGCs) and glial cell line-derived neurotrophic factor (GDNF) in depression and their involvement in neuronal support, intestinal homeostasis maintains and immune response activation. Modulating ENS function, EGCs and GDNF level could serve as novel strategies for future antidepressant therapy.

1. Introduction

Depression is a prevalent mental disorder characterized by persistent feelings of sadness, fatigue, sleep disturbances, loss of appetite and other related symptoms. Data indicates that approximately 280 million individuals worldwide suffer from depression in 2023, accounting for 3.8 % of the global population (Malhi and Mann, 2018). Depression imposes a heavy economic burden (Greden, 2001), with over 700,000 individuals succumbing to suicide annually due to depression-related causes (World Health Organization, 2023). Depression is closely associated with dysfunction of the autonomic nervous system (ANS) (Wang et al., 2013). As the largest branch of the ANS, the enteric nervous system (ENS) is well-connected to the central autonomic network through the motor and sensory pathways of the sympathetic and parasympathetic nervous systems (Goyal and Hirano, 1996). The ENS has been described as the "intestinal brain" or "second brain" and can function independently of the central nervous system (CNS). The gut-brain axis plays a crucial role in maintaining homeostasis and regulating the normal functioning of the body's neurological, endocrine, and immune systems (Lee and Kim, 2021; Chen et al., 2022). As a key connecting component of the gut-brain axis, the ENS is known to contribute significantly to the progression of depression. Its synergistic evolution with the immune system ensures tissue homeostasis and defense (Marklund, 2022). Enteric glia cells (EGCs) are primarily located in the ENS and perform various functions, including supporting and protecting enteric neurons, promoting their regeneration, modulating neuronal mediator expression (Neunlist et al., 2014), maintaining the epithelial barrier integrity (Meir et al., 2021), activating immune responses (Grubišić et al. 2020). The EGC also represents a plentiful reservoir of glial cell line-derived neurotrophic factor (GDNF),which recently attracted significant attention in current depression research (Meir et al., 2021). This review aims to explore the ENS system, focusing on alterations in EGCs and GDNF in depressive disorders through animal models and clinical observations. By investigating their neurobiological mechanisms and potential therapeutic targets, this analysis seeks to illuminate the role of the ENS in depression etiology and management,

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offering insights that may shape future treatment strategies.

2. The pathophysiology of depression

The pathogenesis of depression is complex. Existing hypotheses include the monoamine hypothesis (Hamon and Blier, 2013), the mitochondrial energy metabolism hypothesis (Gebara et al., 2021), the neuroplasticity hypothesis (Tartt et al., 2022), the hypothalamus-pituitary-adrenal (HPA) axis (Kunugi et al., 2010; Li et al., 2020), the gut-brain axis hypothesis (Beurel et al., 2020), and others. The HPA axis, serves as a critical mechanism for triggering stress responses. Activation of the HPA axis induces the secretion of glucocorticoids (GCs), and initiate a negative feedback, loop to terminate the stress response (de Wied et al., 1993; Smith and Vale, 2006; Morais et al., 2021). The vast majority of patients with depression exhibit dysfunction in the negative feedback of the HPA axis (Fries et al., 2023). Additionally, chronic or excessive stress can also result in the suppression of the immune system and exacerbation of inflammatory responses by cortisol (Sorgdrager et al., 2017). Glucocorticoids drive the production of inflammatory subsets in EGC, induce immaturity in intestinal neuron transcription, acetylcholine (ACh) deficiency, and dyskinesia (Schneider et al., 2023).

Gut-brain axis refers to the interaction between the CNS and the ENS (Socała et al., 2021; Zhu et al., 2022). CNS regions, such as the hypothalamus, integrate chronic stress signals and coordinate information transmission to peripheral organs, ultimately impacting the GI tract. This communication takes place through the ANS and the HPA axis (Chan et al., 2023). The ENS engages in the dynamic surveillance and modulation of the intestinal milieu, responding to changes in microbial composition, mucosal barrier integrity, and inflammatory processes (Hao and Stamp, 2023). ENS neurons are equipped with an array of receptors, including Toll-like receptors (TLRs) and nucleotide-binding oligomerization structural domain-like receptors (NLRs), enabling them to detect microbial and injury signals within the gut (Brun et al., 2013). These signals are transmitted to the CNS via the ENS, exerting a profound influence on mood and behavior (Agirman et al., 2021). The ENS also interacts with immune cells in the gut, such as macrophages and dendritic cells. The release of neurotransmitters from enteric neurons, including acetylcholine and neuropeptides, serves to modulate the immune response (Udit et al., 2022). In a reciprocal fashion, cytokines like TNF-α, IL-1β, and IL-6, produced by immune cells, have been implicated in ENS dysregulation, which in turn can impact the blood-brain barrier and contribute to the pathogenesis of depression (El Aidy et al., 2014; Parker et al., 2019; Agirman et al., 2021; Kronsten et al., 2022). GDNF, another neurotrophic factor, has emerged as a potential player in the pathophysiology of depression. Serum GDNF levels in patients with MDD are significantly lower than those in healthy controls prior to treatment (Sharma et al., 2016), which may serve as a promising therapeutic target.

Existing pharmacological treatments for depression, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIS), Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) primarily focus on modulating monoamine neurotransmitter concentrations (Marwaha et al., 2023). Novel treatments, including N-methyl-D-aspartate receptor modulators, anti-inflammatory agents, and psychedelics, are emerging as new intervention targets (Adell, 2020). A significant recent finding suggests that binding to TrkB and allosteric facilitation of BDNF signaling may be the common mechanism for antidepressant action. This discovery could potentially explain how the molecular effects of antidepressants are translated into clinical mood recovery and the pivotal role of neurotrophic factors in depression (Casarotto et al., 2021).

3. Involvement of the ENS in the gut-brain axis and its correlation with depression

3.1. Development and mauration of ENS

The ENS consists of a collection of neurons and glial cells that are responsible for peristalsis, secretion, and blood flow of the GI tract. (Schneider et al., 2018; Yu et al., 2024). It primarily originates from neural crest cells (NCCs) within the vagus nerve segment. These NCCs transform into Enteric Neural Crest-derived Cells (ENCCs) upon migration into the foregut mesenchyme. ENCCs expressing Receptor Tyrosine Kinase (RET) will subsequently colonize the foregut, mid-intestine, and hind intestine at an appropriate rate (Le Douarin et al., 1994; Nagy and Goldstein, 2017; Heanue and Pachnis, 2007). In mice, enteric muscle neuron development precedes submucosal neurons, supporting the "outside-in" ENS development hypothesis (Rao and Gershon, 2018).

In human fetuses, endothelin-receptor-B (ENDR-B) and endothelin-3 (ET-3) are expressed in intestinal neurons and mesenchymal cells, suggesting a role in regulating interactions between neural crest cells and gut mesenchyme, essential for migration (Robertson et al., 1997). Mutations in the EDNRB gene on chromosome 13q22 can disrupt this migration, leading to the absence of intrinsic neurons in the distal intestine, as seen in Hirschsprung's disease (HSCR). Meanwhile, the majority of HSCR cases exhibit mutations in the RET proto-oncogene on chromosome 10q11.2 (Tilghman et al., 2019). RET (Obermayr et al., 2013), in concert with transcription factor SOX10 (Kim et al., 2003), and PHOX2B (Nagashimada et al., 2012; Pattyn et al., 1999) are three crucial central regulators that govern progenitor differentiation. It has also been shown that GDNF supports the survival of multiple neuronal cell types in the developing ENS and activates RET upon binding to members of the glycosylphosphatidylinositol (GPI)-linked family of cell-surface molecules, GFRα-1 and GFRα-2 (Taraviras et al., 1999; Lyu et al., 2024). RET-deficient mice exhibit an almost complete absence of ganglia in specific segments of the GI tract and eliminate the neuronal cell response to GDNF (Schuchardt et al., 1994; Gershon, 2010). GDNF extended survival in three distinct HSCR murine models, ameliorated colonic architecture and functionality, and induced new neuron formation in non-ganglionic intestine cultures (Soret et al., 2020).

Similarly, there are many other neurotrophic factors involved in the development and function of ENS. Neurturin (NRTN) as a member of the GDNF family also binds to GFRα-2 to activate RET (Heanue and Pachnis, 2007). GDNF and NRTN affect different myenteric neurons, respectively (Wright et al., 2021). NT-3, localized to enteric plexuses, intermuscular basal lamina, and along or between circular and longitudinal smooth muscle cells, contributes significantly to ENS development (Hoehner et al., 1996; Chalazonitis et al., 2001). In recent years, it has been demonstrated that cerebral dopamine neurotrophic factor (CDNF), which is expressed in the brain and intestine, is crucial for the development and maintenance of intestinal dopaminergic neurons. CDNF deficiency may lead to degeneration and autophagy in the ENS (Chalazonitis et al., 2020). Ciliary neurotrophic factor (CNTF) provides neuroprotection to a range of neurons in both the central and peripheral nervous systems (Chalazonitis et al., 1998; von Boyen et al., 2002). Innovative protein structures that integrate IL-6 and CNTF functionalities may mitigate these adverse effects (Zheng et al., 2022). The exploration of these neurotrophic factors presents novel avenues for investigating intestinal development and treating gastrointestinal disorders. Nevertheless, further research is warranted to delineate their mechanisms of action within the gut, including their interactions with ENS cells and their specific roles in various intestinal pathologies.

3.2. Structure and function of ENS

The ENS includes primary afferent neurons that exhibit sensitivity to both chemical and mechanical stimuli, intermediate and motor neurons responsible for modulating effector cell activity (Costa et al., 2000).

Anatomically, the ENS is divided into the intermuscular (Auerbach's) and submucosal (Meissner's) plexuses. Positioned between the longitudinal and circumferential muscle layers, the intermuscular plexuses provide motor and secretory innervation to the mucosal layer, regulating secretion, vascular dilation, and contributing to immune responses (Goyal and Hirano, 1996; Ochoa-Cortes et al., 2016; Cryan et al., 2019). Signals originating from the digestive organs are transmitted to the CNS through exogenous primary afferents, triggering reflexes that modulate GI function and contribute to sensations of discomfort, nausea, and pain (Furness et al., 2004). In the submucosal plexus, Intrinsic Primary Afferent Neurons (IPANs) respond to changes in lumen chemistry, specifically short-chain fatty acids, and generate mechanical responses (Kunze and Furness, 1999; Furness et al., 2004; Furness, 2012). The longitudinal and annular smooth muscle layers, as well as the mucosal muscle layer, are primarily innervated by uniaxial excitatory and inhibitory motor neurons with type I morphology (Wood, 2012). The primary neurotransmitters in excitatory motor neurons consist of ACh and bradykinin, while inhibitory motor neurons have been found to contain carbon monoxide (CO), nitric oxide (NO), vasoactive intestinal peptide (VIP), and ATP-like transmitters (Xue et al., 2000; Furness et al., 2014). CO plays a crucial role in regulating GI motility and responses to GI injury (Gibbons and Farrugia, 2004). The production of NO by the ENS serves as a critical regulator of intestinal homeostasis. Aberrant NO signaling significantly impacts intestinal diseases by disrupting intestinal motility, blood supply, and mucosal barrier function (Savidge, 2014). However, it appears that the full effects of NO necessitate the presence of CO (Xue et al., 2000; Farrugia and Szurszewski, 2014). The intrinsic intestinofugal afferent neurons (IFANs) represent a distinct subset of enteric muscle neurons, which are arranged in parallel to the annular muscle fibers and serve as conduits for transmitting mechanical sensory information to sympathetic prevertebral ganglion (PVG) neurons. Upon dilation and activation of the colon, specific inhibitory IFANs release gamma aminobutyric acid (GABA) and ACh at the PVG. This coordinated release leads to an augmented ACh release by cholinergic IFANs in response to colonic distension. Consequently, the reflex arc formed by these interactions serves as a protective mechanism against the abrupt escalation of tension and intraluminal pressure (Szurszewski et al., 2002; Yoo and Mazmanian, 2017).

3.3. The immunol pathways connecting the ENS and the brain

The GI tract harbors the highest density of immune cells in the body, continually exposed to antigens and immunomodulators derived from the diet and symbiotic microbiota (Mowat and Agace, 2014; Cryan et al., 2019). The ENS is indirectly situated in proximity to the diverse collections of immune cells within the innate immune system, enabling the transmission of signals from immune cells to the brain (Schneider et al., 2022). Intestinal neurons secrete colony-stimulating factor 1 (CSF1), a growth factor essential for macrophage development (Muller et al., 2014; Drokhlyansky et al., 2020), while also expressing various neuropeptides, including neuromedin U (NMU) (Cardoso et al., 2017) and calcitonin gene-related peptide (CGRP) (Xu et al., 2019). For example, a subset of sensory neurons (PSN), PSN1, expresses genes that may mediate innate lymphoid cell (ILC) signaling, including CGRP, IL-13 receptor (Il4ra/Il13ra1), and IL-7, a major regulator of ILC and T cells. NMU produced by enteric neurons activates ILC and supports the PSN1-ILC circuit. These key factors are involved in the regulation of tissue homeostasis and immunity (Drokhlyansky et al., 2020).

Afferent neurons communicate with immune cells to suppress intestinal inflammation by inhibiting pro-inflammatory macrophages and regulating M cell function, which in turn limits pathogen invasion and promotes the maintenance of a protective microbiome. Disruption of intestinal homeostasis, leading to increased mucosal permeability or "leaky gut syndrome," can allow bacteria or their components to translocate to tissues, affecting the ENS. Chronic stress may exacerbate intestinal inflammation through ENS-mediated pathways (Seguella et al.). Persistent intestinal inflammation promotes a state of chronic systemic inflammation characterized by elevated serum tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), which compromises the blood-brain barrier (BBB) by increasing the permeability of the brain microvascular endothelial cell layer (Parker et al., 2019). Hyperactivation of microglial cells due to inflammatory stimuli produces excessive cytotoxicity, such as superoxide, NO, and TNFα, which induces significant neurotoxic effects (Block et al., 2007). Recent research posits that the peripheral blood circulating neuronal cell count may serve as a potential clinical biomarker for BBB dysfunction (Zhang et al., 2021b). It can assist in the detection of enteritis-induced BBB disruption and further elucidating the depressive behaviors that may arise from neurological damage to the brain.

3.4. Vagus nerve pathway for ENS to communicate with brain

The ENS, consisting of approximately 200–600 million neurons, is primarily regulated by the vagus nerve (VN), which plays a crucial role in maintaining homeostasis (Mayer, 2011; Furness, 2012; Fülling et al., 2019). Vagal afferent fibres are located within the lamina propria of the GI tract and can interact with gut microbiota metabolites to transmit signals to the brain. This vagal signal affects norepinephrine-producing neurons in the locus coeruleus (LC), which in turn affects the serotonin system in the dorsal raphe nucleus (DRN) (Fülling et al., 2019). Current research shows that chronic stress-induced gut microbiota perturbations activate the VN, leading to serotonin and dopamine neurotransmission deficits in the hippocampus (HPC), neuroinflammation, and impairments in adult HPC neurogenesis, ultimately associated with depressive states in mice (Siopi et al., 2023). In addition, a psychoactive Lactobacillus rhamnosus (JB-1) that affects brain function excites both vagal fibers and IPANs. Intramural synaptic blockade with Ca2+ channel blockers or nicotinic receptor blockade can reduce firing vagal sensory units that were stimulated by luminal JB-1 (Azucena et al., 2014). In mice displaying depressive behaviors, the modulation of tonic vagal inhibition on proinflammatory macrophages was significantly impacted on susceptibility to intestinal inflammation, and the administration of tricyclic antidepressants was observed to restore vagal function and alleviate intestinal inflammation (Ghia et al., 2008). These studies all suggest that the vagus nerve plays a key role in signaling in the gut-brain axis in and is actively involved in the pathology of depression.

Resting vagal tone is typically measured by assessing heart rate variability (HRV). Lower-than-normal baseline respiratory sinus arrhythmia was found to occur in adolescents who were clinically depressed (McVey Neufeld et al., 2024). Thus, VN electrical stimulation has emerged as a potential intervention for the treatment of depression. The exact mechanisms of vagal tone regulation and its role in connecting the gut-brain axis in psychiatric disorders remain an active area of research. Research could focus on the deleterious effects of gut microbiota metabolism in the future, particularly on the gut via IPAN production. Also, strategies to counteract the inhibitory effects of specific neurotransmitters on vagal tone are critical. By disrupting the adverse cyclical interactions in the gut-brain axis that are driven by inflammation, these research advances may alleviate the condition of patients with enterocolitis combined with depression.

3.5. Depression and intestinal inflammation

Studies have shown that patients with IBD often suffer from depression, and those with static IBD and depression at baseline have a poorer prognosis (D. Chen et al., 2023; Piovani et al., 2023). Depressive symptoms affect approximately one-fourth of patients with IBD, with prevalence rising to one-third among those with active disease (Barberio et al., 2021). Patients with depression are at a significantly elevated risk of developing Crohn's disease (CD) and ulcerative colitis (UC) compared to non-depressed individuals (Frolkis et al., 2019; Piovani et al., 2023). It has been hypothesized that maternal prenatal stress affects maternal

intestinal flora by disrupting the HPA axis and increasing circulating cortisol levels, thereby leaving epigenetic memory in ENS and increasing the possibility of IBD (Noemi et al., 2024). TNFα produced during mucosal injury triggers neurodegeneration of the catecholaminergic axons of the colon. This axonal degeneration depletes the neurotransmitter norepinephrine, which would otherwise promote Th17 and ILC3s to express pro-inflammatory IL-17 cytokines (Sun et al., 2021). In certain animal studies, experimentally induced depression elicits intestinal inflammation, such as increased susceptibility to IBD in depressed mice with parasympathetic dysfunction (Ghia et al., 2008), increased release of proinflammatory cytokines from peritoneal macrophages in depressed mice (Ghia et al., 2011), and heightened colon mucosal mast-cell counts in response to fatigue and depression (Piche et al., 2008). Relevant studies have also demonstrated that depression can trigger the reactivation of enteritis (Takahashi et al., 2008; Ghia et al., 2009). Conversely, imipramine, which ameliorates depressive symptoms, exerts inhibitory effects on colitis development and progression (Israelyan et al., 2019). Treatment with tricyclic antidepressants, prevents reactivation of depression-induced colitis and does not impact intestinal inflammation in the absence of depressive conditions (Taché and Bernstein, 2009). These studies suggest a potential contribution of depression to the development of colitis, with the involvement of the vagus nerve in its pathogenesis. Additionally, antidepressants have shown a certain efficacy in mitigating depression-induced intestinal inflammation.

4. The role of egcs in the ENS and their impact on depression

4.1. The origin and composition of EGC

The ENS plays a regulatory role in various gastrointestinal functions through its intricate glial network (Wang et al., 2022). With more than 100 million neurons and over 400 million EGCs (Dowling et al., 2022), the ENS forms a complex system crucial for intestinal homeostasis. EGCs, akin to the CNS's astrocytes in structure and function, envelop and support intestinal neurons, providing protection against oxidative stress by modulating glutathione levels (Wang et al., 2022; Neunlist et al., 2014). Originating from NCCs that migrate to the GI tract during embryonic development, EGCs undergo a well-coordinated process of self-renewal and differentiation, ultimately forming a diverse network comprising different neuronal and glial cell subtypes. However, EGCs exhibit a slower differentiation rate compared to enteric neurons (Sloan and Barres, 2014). There are four distinct subtypes of intestinal glial cells: Type I, located within ganglia, represent protoplasmic astrocytes present in the muscular layer of the intestine. Type II, known as interganglionic EGCs, runs along the neurons of the interganglionic fiber bundles. Type III, referred to as mucosal EGCs or 'mucosal type', display long and branched protrusions that establish contacts with nerve fibers and epithelial cells at the mucosal level. Lastly, Type IV encompasses intramuscular EGCs characterized by their elongated spindle-shaped bipolar projections along nerve fibers in both circular and longitudinal muscles of the intestine (M and A, 1994; Gulbransen and Sharkey, 2012; Boesmans et al., 2022; D'Antongiovanni et al., 2023). These cells express various glial markers, including transcription factors Sox10 and Sox2, calcium-binding protein S100B, and the most recent myelin-associated protein, proteolipid protein 1 (PLP1) (Boesmans et al., 2022; D'Antongiovanni et al., 2023). Specifically, PLP1 is uniquely expressed by glial cells in the adult mouse intestine, further underscoring the distinct phenotypic plasticity and functional heterogeneity of EGCs (Rao et al., 2015).

4.2. Signal transduction between EGC and ENS

EGCs provide structural and metabolic support for neurons and their axons, control synaptic signals and motor patterns (Wang et al., 2022). They support neurons by expressing neurotransmitter precursors, neurotransmitters, and neuroligands, and synthesizing/releasing neurotrophic factors (Xiao et al., 2014). EGCs in the ganglia contribute to neurogenesis and gliogenesis, protect neurons from oxidative stress, and regulate neuronal activity through neurotransmitter receptor signals (D'Antongiovanni et al., 2023). They mediate enteric nerve communication by releasing NO and glutathione, modulating bioavailability of neuroactive substances in the extracellular environment to uphold enteric nerve transmission (MacEachern et al., 2011; Gulbransen and Sharkey, 2012; Brown and Gulbransen, 2018). Specifically, EGCs mount immune response to L-arginine, a key NOS substrate; inhibiting their inducible NOS restores ion transport in colitis mice (MacEachern et al., 2015). Moreover, EGCs exhibit intercellular Ca2+ signaling, transmitting information within ENS (Neunlist et al., 2014; D'Antongiovanni et al., 2023). VIP released by ENS induces transient Ca2+ fluctuations in EGCs, regulating purine release and communication, or inhibiting Ca2+ activity (Fung et al., 2017a; Boesmans et al., 2019).

4.3. Mechanisms of EGC involved in depression

The precise etiology of depression remains elusive, as it involves alterations in neural circuits and neuroendocrine pathways triggered by stress, immune system activation, and intricate interactions between the host and microbiome (Fung et al., 2017b; Hao and Stamp, 2023). EGCs are suggested to be the "missing link" connecting the ENS and CNS, serving as a crucial "gateway" for harmful stimuli from the gut to impact specific CNS regions (Seguella et al.). The ENS transmits stress to the gut (Fyfe, 2023), leading to increased cortisol levels that induce alterations in intestinal wall permeability and a strong inflammatory response (Foster et al., 2017). The knockout of the cortisol receptor in mature glial cells demonstrated a significant reduction in the stress-induced exacerbation of colitis in mice. This finding highlights the essential role of the ENS, particularly EGCs, as a crucial mediator between glucocorticoids from the HPA axis and the modulation of intestinal inflammation (Schneider et al., 2023).

EGCs can perceive environmental context (Bohórquez et al., 2014), and are implicated in modulating sensory signaling from the GI tract to the brain, particularly through the vagus nerve (Kaelberer et al., 2020). Macrophages, which are the predominant leukocytes in the lamina propria of the healthy intestine,(Bain et al., 2014) are closely associated with the ENS (Eyo and Dailey, 2013). During chronic colitis in mice, EGCs can trigger a proinflammatory shift in muscle-derived macrophages by activating Cx43 hemichannels and releasing macrophage colony-stimulating factor (M-CSF). They regulate activation of muscular macrophages and visceral pain through Cx43-dependent release of M-CSF (Grubišić et al. 2020). Reactive gliosis in the CNS or increased intestinal permeability can activate EGCs from the intestinal lumen due to peripheral hypoxia. This activation contributes to the development of a proinflammatory environment, exacerbates impairment of the intestinal barrier, and initiates mechanisms leading to neuronal cell death (Seguella et al.).

During intestinal inflammation, dysfunction of the ENS can disrupt the regulation of tight junctions in the intestinal barrier. Consequently, this process facilitates neurobiology and emotional state of the CNS. EGCs are involved in maintaining intestinal epithelial barrier (IEB) homeostasis through secreted peptides and lipids (Craig et al., 2022; Boesmans et al., 2022). In response to harmful stimuli, EGCs actively participate in the immune recognition process within the intestine, subsequently triggering the innate immune response (Turco et al., 2014). Under harmful stimulation, EGCs can transition into a proinflammatory phenotype, leading to the release of cytokines such as interleukin-1β (IL-1β), IL-6, and interferon-γ (IFN-γ) (Yang et al., 2020; Liu and Yang, 2022; D'Antongiovanni et al., 2023). Studies on Heligmosomoides polygyrus-infected mice have shown that the IFN-γ signaling pathway in EGCs has a protective effect on the intestinal barrier. Knockout of this pathway results in compromised intestinal barrier integrity, dysbiosis, immune and inflammatory activation,

ultimately exacerbating neuronal damage (Progatzky et al., 2021). Additionally, the gut microbiome can produce a variety of neurotransmitters (NTs) that are present in the human brain (Bhatt et al., 2023). Changes in intestinal permeability alter the release and efficacy of monoamine NTs involved in depression. When coupled with dysbiosis, these changes can disrupt the HPA axis, decrease levels of brain-derived neurotrophic factor (BDNF), ultimately manifesting as depressive symptoms (Miller and Raison, 2016; Du et al., 2020).

Enteric neurons and EGCs possess bidirectional differentiation potential during the recovery process from pathological injury. Particularly, EGCs can differentiate into enteric neurons in response to chemically induced tissue injury, inflammation, or infection (Wang et al., 2022). Mature EGCs retain their neurogenic potential while exerting neuroprotective and immunomodulatory effects (Laddach et al., 2023). Remarkably, in an experiment involving lineage tracing of glial cells and detection of Sox10 promoter activity, these cells were observed to express neuronal markers one month after denervation. This intriguing transition implies that these cells likely migrated from adjacent ganglia to the denervated site rather than being derived from proliferating cells (Laranjeira et al., 2011). In the presence of inflammation, newly generated intestinal neurons were found to differentiate alongside cells expressing EGC markers Sox2 and Plp1 (Belkind-Gerson et al., 2017) indicating a potential avenue for therapeutic intervention to facilitate ENS injury repair by modulating EGCs activity.

5. GDNF expression and function in the gut: effects and regulation of depression

5.1. Structure and transduction pathways of GDNF

GDNF was originally discovered in 1991 from a rat glioma cell-line as the first member of GDNF family of ligands (GFLs) (Lin et al., 1993). It is synthesized by a variety of tissues, including brain, gastrointestinal tract, reproductive tissue and skeletal muscle. GFLs include four members: GDNF, neurturin (NRTN), persephin (PSPN), and artemin (ARTN), and they are distant relative of the TGF-β superfamily. The ligands are crucial for neuronal survival, cell proliferation and synaptic plasticity (Airaksinen et al., 1999). The ligand specificity of GFLs is determined by the GDNF family of receptor α (GFRα). The GFRαs receptor consists of GFRα1–4 subtypes, each of which binds to a specific ligand. GDNF specifically binds to GFRα1, NRTN to GFRα2, ARTN to GFRα3, and PSPN to GFRα4. These specific bindings form the high-affinity GFL-GFRα homo-dimer complex, which in turn promotes the aggregation of the two RET receptor molecules (Airaksinen and Saarma, 2002). Activation of RET triggers the phosphorylation of specific tyrosine residues in its tyrosine kinase domain and intracellular signal transduction, such as Ras-MAPK, PI3K-Akt signaling pathways, which occur inside and outside the "lipid raft" and ultimately promote neuronal differentiation and survival (Kaplan and Miller, 2000). Phospholipase C-γ (PLCγ) is a key signaling molecule downstream of RET, which transmits signals by binding to Tyr1015 on the RET receptor (Mulligan, 2014). After RET is activated by GDNF, PLCγ is also activated, triggering the release of intracellular calcium ions and a series of downstream signaling events that are critical for cell proliferation, differentiation, and migration (Kaplan and Miller, 2000). This signal regulates intracellular Ca2+ levels by increasing the level of the inositol 1,4,5-trisphosphate receptor, thus promoting synaptic potentiation, and can also stimulate the phosphorylation of ERK1/2 and CaMKII. A point mutation at Tyr1015 on RET or small interfering RNA gene silencing of PLCγ block the GDNF-induced signaling cascade (Yang et al., 2001; Lundgren et al., 2012). In addition, GDNF, NRTN, and ARTN were found to bind directly to the syndecan-3, which mediates cell diffusion and neurite growth with high affinity and is involved in Src kinase activation. GDNF promotes cell adhesion and spreading through syndecan-3 and activates SFK signaling in an HSPG-dependent manner, without involvement of their conventional receptors (Bespalov et al., 2011). In the presence of GFRα1, NCAM can serve as an alternative receptor for GFL, with GDNF binding to NCAM to promote Schwann cell migration and axon growth in hippocampal and cortical neurons independently of RET (Paratcha et al., 2003). Additionally, GFRα1-NCAM and GDNF-GFRα1-NCAM signaling independently influence both short- and long-range intercellular communication (Sariola and Saarma, 2003). GDNF can also activate Fyn autoenzyme activity and stimulate Erk phosphorylation in RET knockout mouse embryonic cortical neurons to a similar extent (Paratcha et al., 2003).

5.2. Promotion of CNS by GDNF

GDNF is crucial for neural survival and differentiation within the CNS. Although GDNF is exclusively expressed by neurons in healthy brain (Cintrón-Colón et al., 2020), in certain injury or inflammation conditions, other cell types such as astrocytes or microglia may also be induced to express GDNF (Schaar et al., 1994; Cintrón-Colón et al., 2020; Duarte Azevedo et al., 2020; Jin et al., 2022). Studies using various animal models have demonstrated that GDNF gene knockout results in a significant reduction in the number of dopaminergic neurons. This knockout also disrupts the expression of transcription factors essential for their differentiation, such as otp, lmx1b, shha, and ngn1 (Wong et al., 2021).

GDNF promotes neuronal differentiation by attenuating Notch signaling through the regulation of DLK1 expression (Khazaei et al., 2020). Additionally, GDNF leads to increased expression and phosphorylation of tyrosine hydroxylase, which enhances the survival rate of dopaminergic neurons and mitigates neuronal damage (Kasanga et al., 2019). GDNF overexpression leads to an increased number of dopaminergic neurons in the substantia nigra, increased dopamine transporter (DAT) activity, and improved motor behavior (Kumar et al., 2015). Depressive behavior in rats is associated with reduced GDNF expression in the hippocampus (Liu et al., 2012). Studies have found that GDNF family receptorα-1 can be mediated by signaling from neural cell adhesion molecules to induce dendritic growth and dendritic spine formation in the hippocampus (Irala et al., 2016; Li et al., 2023).

Neuroinflammation has been reported to induce GDNF expression in activated astrocytes and microglia, infiltrating macrophages, nestin-positive reactive astrocytes, and neuron/glia (NG2) positive microglia-like cells (Duarte Azevedo et al., 2020). GDNF reduces brain excitability and modulates synaptic plasticity by enhancing GABAergic inhibitory transmission in the hippocampal network, thereby mitigating neurological disease episodes (Mikroulis et al., 2022).

GDNF is also known to play a role in regulating the permeability of BBB (Huang et al., 2019). It increases claudin-5 expression via the PI3K/AKT/FOXO1 and MAPK/ERK pathways. Meanwhile, GDNF promoted VE-cadherin expression by activating PI3K/AKT/ETS1 and MAPK/ERK/ETS1 signaling, ultimately enhancing the integrity of the blood-brain barrier (Yang et al., 2024). Sig-1 R activation can upregulate GDNF or promote the GDNF–GFRα1 combination with RET to protect the BBB (Liu et al., 2022a). GDNF exhibits neuroprotective effects in experimental models of amyotrophic lateral sclerosis (ALS) and retinal degeneration (Laperle et al., 2023). Its upregulation modulates microglia activation and acts as a negative regulator of neuroinflammation (Rocha et al., 2012). These findings imply that GDNF could be utilized in cellular and gene therapies for a broad spectrum of neurodegenerative diseases. In addition, it is important to mention that some studies reporting GDNF expression in some cell may be based on non-specific staining techniques. False positives results can occur due to cross-reactivity or background staining. Future studies should consider using multiple, complementary techniques to confirm cellular localization of GDNF.

5.3. Regulation of ENS function by gdnf and other neurotrophic factors

GDNF modulates ENS function, with GFRa1 mediating distinct

effects on approximately 50 % of myenteric neurons, as shown by calcium imaging, and impacts smooth muscle contractions (Wright et al., 2021). The ingestion related release of VIP from ENS modulates the homeostasis of $CCR6^{+}$ ILC3 expressing VIP receptor 2 (Seillet et al., 2020). Furthermore, electroacupuncture induces the α7 nicotinic acetylcholine receptor via a central-cholinergic pathway, promoting GDNF release from EGCs and safeguarding intestinal neuronal function, thereby ameliorating GI motility (Zhang et al., 2024). Toll-like receptor 2 (TLR2) is located principally in the intestinal mucosal layer and maintains barrier integrity as well as modulates immune responses (Cario et al., 2007). The disruption of the ENS in TLR2 knockout mice has been linked to a deficiency in GDNF or the GFRa2 receptor (Rossi et al., 1999; Anitha et al., 2006). GDNF deficiency is associated with innervation defects, impairing the coordinated control of GI motility. Therapeutic GDNF administration may significantly enhances ENS function and intestinal motility. Rectal GDNF application in a ganglionic segments stimulates intestinal glial cell proliferation and production (Soret et al., 2020).

ENS neurons innervate Peyer plaques together with exogenous sensory and nociceptive DRG neurons (Kulkarni et al., 2021). DRG neurons innervate the gut and project nociception into the spinal cord (Grundy et al., 2019). Following nerve injury, the expression of GDNF associated with DRG and proximal regeneration of sensory neurons at the site of injury is decreased by retrograde axonal signaling of molecular kinases. Upregulating GDNF expression can reduce the inflammation and pain of nerve stump (Wang et al., 2023). Similarly, other GFLs such as ARTN and NRTN also affect DRG functions. ARTN was found to promote neurite growth and actin polymerization in mature DRGs by influencing the transcription of many target genes and to stimulate topographically correct regeneration of DRG axons in rodent dorsal root crushing models (Zhu et al., 2020).

5.4. *Mechanisms of GDNF regulation of depression through neurotransmitters*

Numerous studies have shown that antidepressants improve mood states by regulating neurotransmitters in the brain and can significantly improve GDNF levels in the body. Monoamine theory posits that depression results from a deficiency in the neurotransmitters serotonin (5-HT), norepinephrine (NA), and dopamine (DA) (Hamon and Blier, 2013). Meanwhile, gamma-aminobutyric acid (GABA) and glutamate have been implicated in the etiology of depression (Catena-Dell'Osso et al., 2013; Pehrson and Sanchez, 2015). GDNF is involved in the development of depression through interactions with these neurotransmitters.

Acute central administration of GDNF to ASC mice with depressive behavior produced anxiolytic effects, resulting in a significant decrease in 5-HT1A and 5-HT2A receptor gene expression in the hippocampus and an increase in 5-HT1A in the midbrain and 5-HT2A receptor gene expression in the frontal lobes (Naumenko et al., 2013). However, other studies have shown that GDNF upregulates the expression of 5-HT2A receptor genes in the prefrontal cortex, but has no effect on the hippocampus and midbrain (Tsybko et al., 2014). Tph-2 represents a sensitive marker of functional activity in the brain's 5-HT system, and GDNF-induced increases in midbrain Tph-2 mRNA levels suggest activation of the 5-HT system (Popova and Kulikov, 2010). 5-HT, in turn, controls the expression of GDNF by specifically increases GDNF mRNA levels in a dose- and time-dependent manner (Tsuchioka et al., 2008; Day et al., 2014), inducing GDNF mRNA expression through 5-HT2 R-mediated FGFR2 transactivation (Tsuchioka et al., 2008). Excess 5-HT alters mesencephalic neuronal cell differentiation, shown by reduced cell aggregation and altered expression of GDNF and Neu-N proteins (Menegola et al., 2004).

Chronic "unpredictable" stress makes LC-NE system dysregulation, impairing the adaptation system. The CRH-NE-CRH feed-forward system progressively augments the stress response with repeated exposure

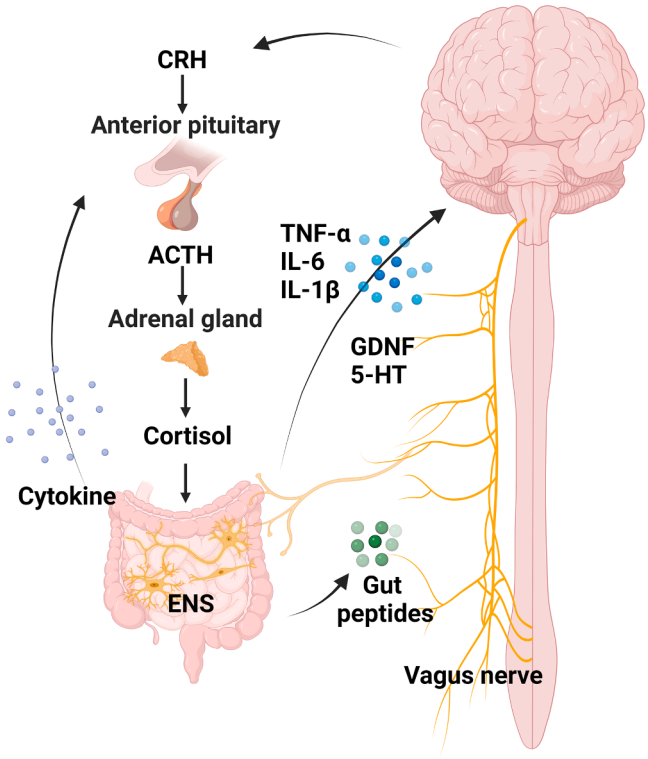

Fig. 1. The gut-brain axis. Under stress and inflammatory stimuli, inflammatory factors in the gut can influence the release of corticotropin-releasing hormone (CRH) from the hypothalamus via activation of the HPA axis, which in turn stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH), ultimately leading to an increase in adrenocorticotropic hormone secretion (e.g. cortisol). Inflammatory factors in the gut such as TNF-α, IL-6 and IL-1β This response can be further modulated through the vagus nerve pathway. The vagus nerve is the main parasympathetic nerve that interconnects with the brain through the gastrointestinal tract. It communicates closely with neurons and glial cells in the gut and regulates intestinal motility, inflammatory responses and mucosal barrier function by releasing neurotransmitters such as acetylcholine. Gut-derived 5-HT activates vagal pathways. In addition, gut-derived glial cell-derived neurotrophic factor (GDNF) has been found to play an important role in the vagal pathway. GDNF promotes the growth and regeneration of vagus nerves and maintains the homeostasis of the gut-brain axis by suppressing inflammatory responses and protecting neuronal function.

(Perrelli et al., 2024).Research has shown the development of the NE-LC-hippocampus pathway is dependent on the presence of GDNF using GDNF knockout models (Quintero et al., 2004). GDNF prevents NA neuronal degeneration in vivo (Arenas et al., 1995), and participates in the modulation of depression by mediating NA in the HPA axis. Genetic loss of GDNF decreases the number of tyrosine hydroxylase (TH) neurons in the pontine A5 noradrenergic cell group, and inhibits medulla oblongata function (Huang et al., 2005).

GDNF is also involved in supporting specific DA neurons (Pascual et al., 2011). Bilateral GDNF injections into the striatum of neonatal rats show that striatal GDNF regulates the production and release of neurotransmitters by DA neurons and 5-HT neurons during development (Beck et al., 1996). A 2- to 3-fold increase in brain GDNF levels are sufficient to raise striatal presynaptic dopamine levels and reduce those in the prefrontal cortex. Adenosine A2a receptors may mediate these GDNF-induced dopamine abnormalities (Mätlik et al., 2022). In the striatum injected with (AAV)-GDNF, transplanted mDA neurons lengthened axons by 8 mm and innervated host forebrain structures including the striatum (Moriarty et al., 2022). In addition, GDNF increases the expression of D1 and D2 receptor genes in the nucleus ambiguus of ASC mice, with long-term genotype-dependent effects on depressive-like behaviors and the brain dopamine system (Naumenko

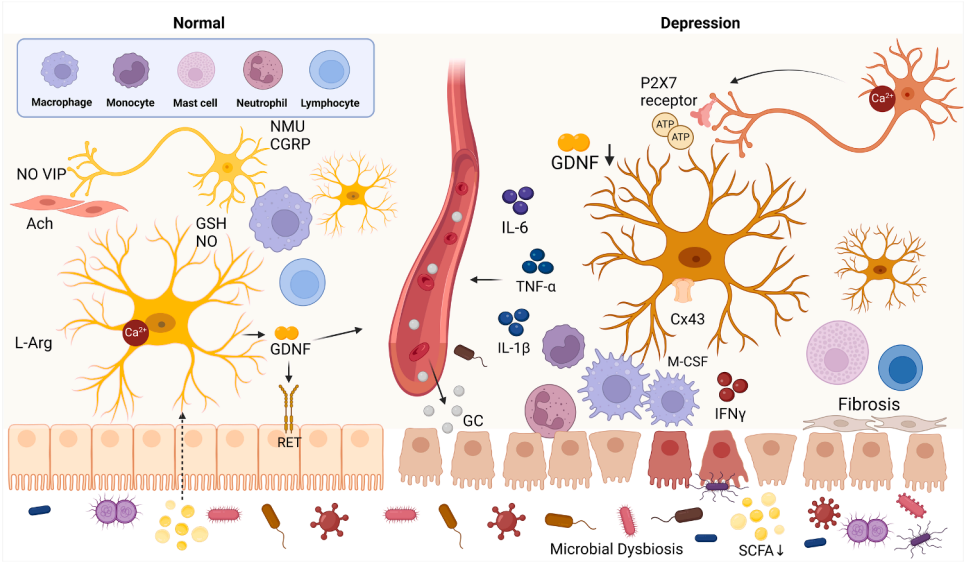

Fig. 2. Interaction at gut. In normal state, enteric neurons express Neuromedin U (NMU), Calcitonin Gene-related Peptide (CGRP). Vasoactive Intestinal Peptide (VIP) released by enteric nerves induces Ca2+ transients.EGC releases NO, glutathione, and enteric nerve communication, where L-arginine (L-Arg) is a substrate required for NO synthesis. The release of GDNF from enteric glial cells is involved in the maintenance of intestinal barrier homeostasis, and some of the GDNF enters the peripheral circulation through the bloodstream. Short-chain fatty acids (SCFA) produced by anaerobic bacteria or yeasts in the gut through fermentation of dietary fibre promote EGC maturation and lead to the release of intestinal peptides, which influence the activity of the gut-brain axis. In depressed states, the HPA axis negative feedback is imbalanced, cortisol released into the gut increases, and the gut barrier receives disruption. Microbial metabolites enter the gut through the disrupted intestinal barrier. EGCs can drive a shift in the pro-inflammatory phenotype of myofibroblast macrophages through the mechanism of Cx43 hemichannels and macrophage colony-stimulating factor release. Macrophages, along with other immune cells, secrete inflammatory factors into the bloodstream. Inflammation releases ATP into the extracellular compartment, and these released ATP molecules can bind to the P2X7 receptor on the enteric nerve, thereby activating the receptor. Long-term chronic inflammation leads to fibrotic thickening of the intestinal wall.

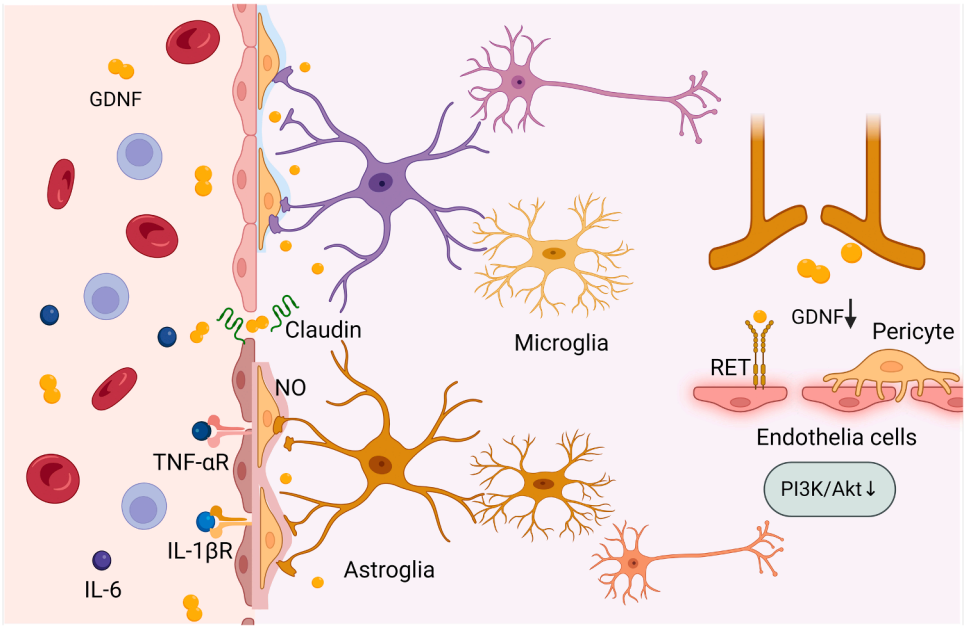

Fig. 3. Interaction in brain. Under normal conditions, GDNF regulates blood-brain barrier (BBB) and blood-nerve barrier (BNB) permeability. GDNF secreted from brain and BNB-derived peripheral nerve pericytes enhances BBB and BNB function by upregulating the expression of claudin-5, the most important component involved in maintaining the BBB. In the depressed state, GDNF is reduced and Circulating Endothelial Cells (CEC) at the blood-brain barrier are activated by circulating peripheral inflammatory chemokines, releasing pro-inflammatory mediators into the brain. CEC have TNF-α (Tumor Necrosis Factor, TNFα) and IL-1β receptors. Their activation produces intracerebral synthesis of NO and prostaglandin-like compounds.45 Both NO and TNFα are highly neurotoxic.81 This may lead to neuronal cell death, loss of blood-brain barrier integrity, and brain injury.

et al., 2014).

GDNF increases neurite length and number in GABA-ir neurons (Ducray et al., 2006). In cerebral cortex cultures, GDNF also induces an increased proportion of GABA-ir cells (Pozas and Ibáñez, 2005). The GDNF-GFRα1 and HGF-MET signaling pathways promote the expression of cortical GABAergic interneurons. The autoinhibition of MET/HGF, a transmembrane receptor crucial for the development of these interneurons, enhances the activity of GDNF on MGE neurons. This

autoinhibition also increases the expression of GFRα1 mRNA in MGE cells. This process is dependent on endogenous GDNF and GFRα1 (Perrinjaquet et al., 2011). In both normal and damaged conditions, 95 % of GDNF-expressing cells in the nascent striatum are small serotonin-positive GABAergic interneurons (Hidalgo-Figueroa et al., 2012). Reduced levels of GDNF induce excess glutamate release and dysregulation of glutamate transporter-1, causing excitotoxicity in the substantia nigra that precedes dopaminergic degeneration (Farrand et al., 2015). GDNF is required to phosphorylate PI3K and Src to upregulate the glutamate transporter proteins GLAST-1 and GLT-1, thereby protecting the CNS (Koeberle and Bähr, 2008).

5.5. GDNF reduces intestinal permeability and inhibits intestinal inflammatory responses thus contribute to depression

The maturation of intestinal epithelial barrier (IEB) is regulated by GDNF receptor RET, as EGC-mediated IEB homeostasis depends on it. When GDNF is depleted in EGC supernatants, knocked down in EGCs, or when the GDNF receptor RET is obstructed, it hinders IEB maturation (Meir et al., 2021). B Bridges in the intestinal epithelium consist of calcineurin-type adhesion molecules DSG2 and DSC2. GDNF secreted by EGCs promotes intestinal barrier maturation by regulating DSG2 in vitro (Meir et al., 2019). Morphological alterations in EGCs can influence the initiation or persistence of GI disorders and their associated symptoms (D'Antongiovanni et al., 2023). In patients with IBD, DSG2 is reduced by RET-p38 MAPK-dependent keratin phosphorylation. GDNF attenuates inflammation-induced impairment of IEB function through RET/MAPK pathway (Meir et al., 2019).

As mentioned above, gut inflammation increases intestinal permeability and increasing susceptibility to depression (Beurel et al., 2020). GDNF, serves as an important mediator between EGCs and mucosal epithelial cells, is involved in the regulation of intestinal barrier function. In patients with ulcerative colitis and Crohn's disease, EGCs are activated during inflammation, leading to fibrotic remodeling of the intestinal wall, increased GFAP- and S100-β-positive glial cells, and higher GDNF expression in the inflammatory region (D'Antongiovanni et al., 2023). This activation reduces the permeability of the intestinal epithelial barrier during inflammation. GDNF is also capable of inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-1β, as well as the infiltration of neutrophils, thereby suppressing the inflammatory response in the intestinal tract (Zhang et al., 2010a). Overall, it significantly restores the barrier function of the epithelium by reducing epithelial permeability and inhibiting inflammatory responses, effectively combating DSS-induced colitis (Zhang et al., 2010b). The release of NO from EGCs and prostaglandin E2 also contributes to inhibiting the inflammatory response and maintaining intestinal immune homeostasis (Progatzky et al., 2021).

6. Potential role of ENS and GDNF in the treatment of depression

There are various treatment approaches available for depression targeting the gut-brain axis (Craig, 2005; Scassellati et al., 2021; Zhang et al., 2021a; Winiarska-Mieczan et al., 2023). Existing research has shown that regulating EGC and GDNF has achieved good therapeutic effects in depression treatments.

PD depression (DPD) occurs in up to 40 % of people with PD (Aarsland et al., 2012; Ravina et al.). Reduction of connectivity in cortical–subcortical limbic circuits and imbalance in dopamine, serotonin, and noradrenergic hormones are known to be a primary cause of depression in DPD (Evans and Barker, 2008; Laux, 2022; Yin et al., 2022). GDNF is a potent inducer of dopaminergic neuron survival and growth in animal models of PD (Evans and Barker, 2008). SINEUP-GDNF, an innovative technology, has been shown to increase endogenous GDNF levels. This increase ameliorates motor deficits and neurodegeneration in dopaminergic neurons in a mouse model of PD (Espinoza et al., 2020). Additionally, a clinical trial involving brain GDNF administration in PD patients demonstrated significant improvements. Patients experienced an average 38 % improvement in motor function and an 8 % increase in the Unified Parkinson's Disease Rating Scale (UPDRS) total score compared to conventional treatment (Gash et al., 2020). Reduced dopamine levels within the mPFC were associated with decreased inhibitory activity, apathy, and anhedonia. GDNF has been shown to increase the expression of PSD95 and synapsin-1, enhancing the density of dendritic branching and dendritic spines. These changes help activate the DRD1-mediated adenylate cyclase-cAMP-PKA pathway in the mPFC, which in turn exerts an antidepressant effect (Liu et al., 2024). Adeno-associated viruses (AAVs) serve as gene therapy vectors for depression treatment (O'Carroll et al., 2021). After peritoneal injection of AAV-GDNF, GDNF promoted intestinal motility in a PD rat model by inhibiting EGC activation and CX43 expression, thereby alleviating the depressive state (Xiaoling et al., 2024).

The most compelling evidence for GDNF's role in depression is the low peripheral levels of GDNF, which can be effectively modulated by antidepressants (Hisaoka et al., 2004; Kohl et al., 2012; Kotyuk et al., 2013a; Sharma et al., 2016; Liu et al., 2022b). In addition, there was a significant positive correlation between baseline GDNF plasma levels and cognitive functions (e.g., information processing speed, working memory capacity, and alertness) in patients with MDD. Genetic sequencing of clinical patients suggests that GDNF polymorphisms are associated with depression, those with the rs3812047 G allele of GDNF and exhibited significantly higher scores (Kotyuk et al., 2013b; Liu et al., 2022b). Chronic stress leads to reduced GDNF transcript and protein levels in BALB mice, which can be restored by overexpressing GDNF in the Nucleus Accumbens (NAc) (Miller, 2011). Glucocorticoids inhibit GDNF expression and release, and chronic ultra mild stress leads to increased DNA methylation accompanied by histone modifications, ultimately contributing to a depression-susceptible phenotype in BALB mice (Uchida et al., 2011). Treatment with valproic acid (VPA) has been shown to increase GDNF mRNA expression in C6 cells in a concentration-dependent manner (Castro et al., 2005).

Research consistently affirms the association between depressive conditions and gut microbial homeostasis perturbations. (Ballesio et al., 2024). ENS and GDNF participate in the regulation of depression by affecting intestinal homeostasis. The overall prevalence of depressive symptoms in IBD exceeds 20 % (Bisgaard et al., 2022). The inhibition of EGCs activity can ameliorate the anxiety- and depression-like behaviors caused by IBD (Li et al., 2024). In the early therapeutic stages of Crohn's disease, neuroprotective strategies and gene therapy targeting EGCs have shown efficacy. The upregulation of NOS_2 in EGCs can lead to increased NO production, which is closely associated with intestinal inflammation (Brown et al., 2016). The glial calcium response in EGCs relies on intercellular signaling facilitated by glial connexin-43 channels (McClain et al., 2015; Grubišić and Gulbransen, 2017). Modulating connexin-43, P2X7 receptors, and membrane connexin-1 channels could help attenuate intestinal inflammation. (Gulbransen and Christofi, 2018). Foxp3, a specific transcription factor controlling Tregs, promotes an innate immune response in the brain, leading to anxiety- and depression-like behaviors (Yang et al., 2023). EGCs and their secreted GDNF induce T-cells to differentiate towards $Foxp3^{+}$ Treg and increase IL-10 secretion, alleviating inflammation in colitis caused by DSS.

While current evidence implicates reduced EGC-derived GDNF in the neuropathology of depression, several key questions remain unanswered. Future studies should elucidate the precise molecular mechanisms by which GDNF deficiency contributes to depressive neuropathologies, such as reduced neuroglia density, cortical atrophy, and dysregulated neurogenesis. Moreover, determining the regional specificity of GDNF alterations within the brain could inform the development of targeted therapeutic approaches. Elucidating the interplay between GDNF and other neurotrophic factors, neurotransmitter systems, and inflammatory mediators will provide a more comprehensive understanding of depression pathogenesis. Ultimately, preclinical

studies exploring the therapeutic potential of GDNF augmentation, either through exogenous administration or by modulating endogenous EGC function, could pave the way for novel antidepressant strategies.

7. Conclusion

This review delves into the connection between depression and the ENS, with a specific focus on the HPA axis, which is among the most prominent hypotheses of depression and highlights the crucial roles of the EGC and GDNF in its progression. The gut-brain axis is a sophisticated interconnected system comprising neural signaling networks, immune signaling networks, all of which are pertinent to the pathophysiology of depression. Notably, the vagus nerve pathway has garnered increasing attention in research. The gut-brain axis is emerging as a novel paradigm, where heightened intestinal barrier permeability and inflammation in the gut lead to HPA axis hyperactivity upon its activation, ultimately culminating in neuroendocrine disorders. EGC, a constituent of the ENS, secrets molecules with antioxidant and anti-inflammatory properties to bolster the integrity of the intestinal barrier by upregulating the expression of tight junction proteins between intestinal epithelial cells. GDNF, a key mediator released by EGCs, plays a crucial role in surveilling of enteric neuroglia by suppressing inflammatory responses, improving intestinal flora, decreasing intestinal permeability, preserving mucous membrane integrity, and modulating the immune system. These significant targets could be novel ideas for the future treatment of depression and offer more possibilities for the treatment of depression.

Author contributions

Liang CY, Wei SJ and Ji YL conceived the manuscript topic and structural design. Jing X and Liang CY prepared the figures. Liang CY, Wei SJ and Ji YL drafted and finalised the manuscript with critical input and revisions from Yan FX, Lin JY, Jiao WL, and Li ZY.

Declaration of Competing Interest

All authors declare no conflict of interest.

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Data Availability

No data was used for the research described in the article.

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