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# Alleviation of Depression by Glucagon-Like Peptide 1 Through the Regulation of Neuroinflammation, Neurotransmitters, Neurogenesis, and Synaptic Function

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Depression has emerged as a major cause of mortality globally. Many studies have reported risk factors and mechanisms associated with depression, but it is as yet unclear how these findings can be applied to the treatment and prevention of this disorder. The onset and recurrence of depression have been linked to diverse metabolic factors, including hyperglycemia, dyslipidemia, and insulin resistance. Recent studies have suggested that depression is accompanied by memory loss as well as depressive mood. Thus, many researchers have highlighted the relationship between depressive behavior and metabolic alterations from various perspectives. Glucagon-like peptide-1 (GLP-1), which is secreted from gut cells and hindbrain areas, has been studied in metabolic diseases such as obesity and diabetes, and was shown to control glucose metabolism and insulin resistance. Recently, GLP-1 was highlighted as a regulator of diverse pathways, but its potential as the therapeutic target of depressive disorder was not described comprehensively. Therefore, in this review, we focused on the potential of GLP-1 modulation in depression.

Keywords: depression, glucagon-like peptide-1 (GLP-1), neuroinflammation, neurogenesis, synaptic plasticity

## INTRODUCTION

Depression is emerging as one of the main causes of morbidity and mortality globally, and the number of individuals reported to be afflicted with the disorder continues to increase (Ledford, 2014; Gerhard et al., 2016). Even though extensive research has been conducted, depression remains incompletely understood owing to the scarcity of biomarkers and the heterogeneity of precipitating causes, such as chronic stress (Kessler et al., 2005; Krishnan and Nestler, 2008). A recent study investigated the relationship between depression and metabolism, and found that metabolites, such as advanced glycation end products, in patients with depression are altered compared to those in controls (Setoyama et al., 2016; Akimoto et al., 2019).

Glucagon-like peptide-1 (GLP-1) is a peptide hormone primarily synthesized in the gut that circulates through the blood, and plays a critical role in the regulation of glucose metabolism in the gut-brain axis. GLP-1 is also secreted by a small population of neurons in the hindbrain (Richard et al., 2015). GLP-1 receptors (GLP-1Rs) are distributed across various organs including the pancreas, lung, stomach, intestine, kidney, heart, and diverse brain regions (Bullock et al., 1996; Li et al., 2009; Campbell and Drucker, 2013; Heppner et al., 2015a).

In the central nervous system (CNS), GLP-1 and GLP-1R agonists are diffused into the cerebrospinal fluid (CSF) and the brain as demonstrated in rodent models (Wang et al., 2015), and increased GLP-1 concentration in the brain is thought to influence brain function in the hippocampus (Kastin et al., 2002; Kastin and Akerstrom, 2003; McClean et al., 2010; Hunter and Holscher, 2012). Glucose-insulin metabolic homeostasis is important for the gut-brain axis because glucose is used as the main source of energy in the brain (Weber, 2016). Major incretins such as GLP-1 and GIP can control appetite by reducing feelings of hunger and by increasing satiety and have a regulatory effect on glucose homeostasis through the reduction of blood glucose levels and insulin release (**Figure 1**) (Edholm et al., 2010; Duarte et al., 2013).

Although previous studies have demonstrated that GLP-1 has positive effects on attenuating neuropathology, its function and specific actions in CNS diseases have not been reviewed comprehensively. Here, we review the therapeutic effects of GLP-1 on depression from a variety of perspectives and highlight the promising, beneficial roles of GLP-1 as the therapeutic regulator of impaired neurogenesis, neuroinflammation, imbalance of neurotransmitter secretion, and synaptic dysfunction in the depressive brain.

## WHAT IS GLP-1?

GLP-1 is a 30 amino acid-long peptide hormone mainly produced in the intestinal L-cells of the gut that is secreted into the blood (**Figure 1**) (Habib et al., 2013; Richard et al., 2015). GLP-1 is also secreted from microglia (Kappe et al., 2012) and specific neurons of the nucleus tractus solitarius (NTS)
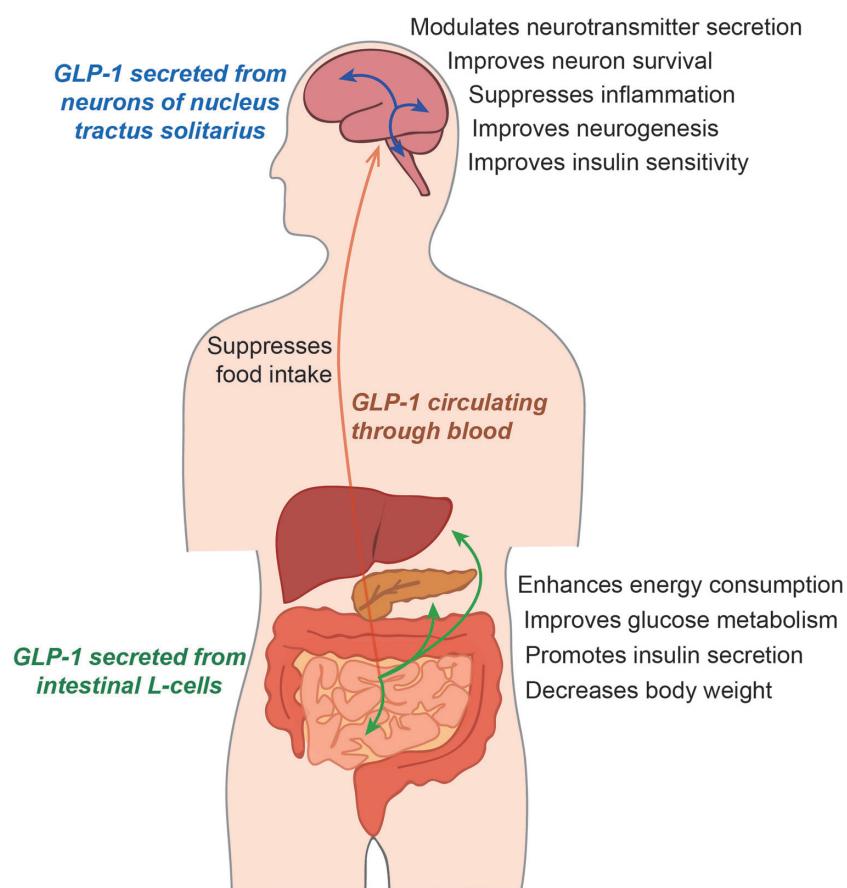


**FIGURE 1 |** The function of glucagon-like peptide 1 (GLP-1) in humans. GLP-1, secreted from the intestinal L-cells, circulates the whole body through the blood. GLP-1 influences energy metabolism and glucose metabolism by regulating the insulin level. In the brain, GLP-1 secreted from intestinal cells can be absorbed into the brain, and the GLP-1 secreted from neurons remains in the cerebrospinal fluid. GLP-1 can control the secretion of various neurotransmitters and the progression of neuroinflammation, and can regulate insulin sensitivity in the brain.

(Alhadeff et al., 2012). Activation of these GLP-1-secreting neurons is regulated by the glucose level. The neurons innervate several brain regions including the hypothalamus, thalamus, paraventricular nucleus, cortex, and arcuate nucleus (Cork et al., 2015), and convey vagal motor information to the pancreas (Parker et al., 2010; Kappe et al., 2013; Calsolaro and Edison, 2015; Richard et al., 2015). GLP-1 has been reported to improve glucose-dependent insulin action through the G-protein-coupled receptor, GLP-1R (Drucker and Nauck, 2006).

GLP-1 is involved in the regulation of energy balance (Holst, 2007), and its activation and subsequent binding to the GLP-1R reduces food intake and, consequently, body weight (Turton et al., 1996). In the CNS, GLP-1Rs are expressed by neurons in the hippocampus, which is known to be a cognition-related brain region, and have been observed in neocortical pyramidal neurons (Hamilton and Holscher, 2009). In the brain, GLP-1 secreted from intestinal cells can be absorbed into the brain, and GLP-1 secreted from neurons remains in the CSF (Cabou and Burcelin, 2011). GLP-1 can control the secretion of various neurotransmitters, the progression of neuroinflammation, and the increase in insulin sensitivity in the brain (Athauda and Foltynie, 2016). GLP-1 is also thought to play an important role in glucose metabolism and neuronal function, including synaptic plasticity and neuronal metabolism, in the brain (Holscher, 2012). One study demonstrated that overexpression of GLP-1R in the hippocampus leads to an improvement in memory function (McClean and Holscher, 2014; Hansen et al., 2015). Microglia are also known to secrete GLP-1 (Kappe et al., 2012). Furthermore, the activity of GLP-1 secreting neurons is regulated by the glucose level (Parker et al., 2010; Kappe et al., 2013).

A recent study demonstrated that GLP-1 has a neurotrophic effect and promotes neurotrophic processes in the brain (Mainardi et al., 2015). Robinson et al. demonstrated that a mixture of GLP-1 agonists boosts memory and improves insulin action in the brain (Robinson et al., 2019). Exendin-4, a stable synthetic form of GLP-1, is commonly used clinically for diabetes treatment because GLP-1 has a short half-life (Drucker and Nauck, 2006; Heppner et al., 2015b). Furthermore, exendin-4 can cross the blood-brain barrier (Kastin and Akerstrom, 2003) and has a neuroprotective role in some neurological disorders (Holscher, 2010; Candeias et al., 2015). Clinically, GLP-1 analogs have been developed to treat diabetes and obesity, given that they have beneficial effects on blood glucose control and on the cardiovascular system. Liraglutide is a GLP-1 analog used in clinically obese patients for reducing body weight (Crane and McGowan, 2016). The effects of weight loss were observed upon daily liraglutide injection (Mora and Johnson, 2017), oral administration of liraglutide (3 mg) (Manigault and Thurston, 2016), and subcutaneous treatment of liraglutide for 20 weeks (1.2 to 3 mg) (Astrup et al., 2009). An interesting study also showed that oral administration of GLP-1 could reduce depression risk caused by hyperglycemia in a patient with type 2 diabetes (Onoviran et al., 2019).

In the next part of this review, the diverse roles of GLP-1 in the depressive brain will be discussed. Moreover, in each section, we will describe the various anti-depressive effects of GLP-1 in the CNS based on recent evidence.

## OVERVIEW OF DEPRESSION

Major depressive disorder (MDD) is a highly prevalent mood disorder characterized by ruminative thoughts, impaired cognition and anhedonia, and attentional control deficits (Marchetti et al., 2012; Disease et al., 2016). Depression is thought to arise from a combination of genetic background and environmental stressors (Belmaker and Agam, 2008). Depression is considered a severe disorder because the features of depression negatively influence the quality of life of patients and their families, and are associated with increased economic and mental health burden (Hamilton et al., 2015).

Some reports have demonstrated that more than 50% of patients with depression experience chronic and recurrent problems throughout their lifetime, and that depressive symptoms can gradually aggravate and lead to suicide if patients are not treated with proper drugs or counseling (Monroe and Harkness, 2005; Rush et al., 2006). For these reasons, patients with depression must be accurately treated, and research aimed at preventing the onset of depression is therefore critical.

Depression is a disease that is highly related to neuroinflammation, neurotransmitter imbalance, blood-brain barrier hyperpermeability, deficits in neurogenesis, and synaptic dysfunction (Najjar et al., 2013; Felger and Treadway, 2017). One study observed that patients with depression showed impaired neurogenesis, neural growth retardation, and synaptic plasticity reduction (Serafini, 2012). In particular, the prefrontal cortex (PFC), amygdala, and hippocampus are crucial for regulating emotion, stress responses, and motivation. In patients with depression, the function of the PFC and hippocampus is disrupted, whereas the amygdala is hyperactivated (Serafini, 2012).

Although numerous anti-depressive treatments are available, 30% of patients diagnosed with depression do not experience positive therapeutic effects with these therapies (Al-Harbi, 2012). Hence, the mechanism of depression must be elucidated to facilitate the discovery of novel and effective anti-depressive therapies.

The gut is a key member of the gut-brain axis owing to its own enteric nervous system and its independent responses to the exterior environment and stress (Rao and Gershon, 2016). In recent years, the gut-brain axis has been increasingly considered a promising topic for the study of CNS-related diseases because the gut microbiota and gut hormones have been shown to interact with other organs including the brain (Knight et al., 2017), although the mechanisms involved in gut homeostasis and brain function are as yet uncharacterized (Collins and Bercik, 2009; Neufeld and Foster, 2009). Previous studies have demonstrated that the regulation of the immune system, endocrine system, and nervous system is strongly involved in the connection between the gut and the brain (Forsythe et al., 2010).

Several studies have shown that depressed patients have impaired gut-brain axis metabolism, appetite disturbances, and gut hormone abnormality (Collins and Bercik, 2009; Evrensel and Ceylan, 2015; Jiang et al., 2015). For these reasons, the current view of depression as an exclusively neurological

disorder was expanded to consider it a systemic disease, given that depression involves the impairment of the hypothalamic–pituitary–adrenal (HPA) axis, immune dysregulation, and disturbance of the gut-brain axis (Maes et al., 2011; O'Mahony et al., 2015). Various factors and signaling pathways are linked to gut-brain axis dysfunction that putatively leads to depression (Scott et al., 2013).

Although there is evidence associating depression with the gut, the action of the gut hormone GLP-1 is still not fully understood in the depressive brain. In the next section, we will focus on the diverse roles of GLP-1 in depression (**Table 1**).

## Neuroinflammation in Depression and Its Relation to GLP-1

The immune system in the CNS has been shown to regulate brain development, neurogenesis, mood, and behavior (do Prado et al., 2016; Zheng et al., 2016; de Miranda et al., 2017). Over the past two decades, several studies have indicated that neuroinflammation is a critical reason for the onset, deterioration, relapse, and maintenance of depression (**Figure 2**) (Kopschina Feltes et al., 2017; Paudel et al., 2018; Woelfer et al., 2019). A recent study demonstrated that neuroinflammation could evoke depressive symptoms such as anhedonia and motor retardation (Felger and Treadway, 2017). Chronic neuroinflammation has been reported to contribute to serotonergic, dopaminergic, and noradrenergic dysfunction in the brain (Song and Wang, 2011) and to lead to chronic immune dysregulation (Carvalho et al., 2013).

Previous studies found that pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, IL-1β, and C-reactive protein (CRP), are markedly increased in the blood and CSF of patients with depression (Hestad et al., 2016; Smith et al., 2018). IL-1, IL-6, IL-1β, TNF-α, and CRP are considered markers of the initiation, relapse, and

progression of depression (**Figure 2**) (Haapakoski et al., 2016). Clinically, elevated levels of CRP and IL-6 were observed in patients with depression when compared to healthy subjects (Goldsmith et al., 2016) and were associated with cognitive symptoms in such patients (Gimeno et al., 2009). Furthermore, these increased levels of pro-inflammatory cytokines resulted in an increase of corticotropin-releasing hormone activity and hyperactivity of the HPA axis in most patients with depression (Kopschina Feltes et al., 2017). Excessive pro-inflammatory cytokines suppress the negative feedback of the HPA axis, boost the permeability of the blood-brain barrier, decrease the synthesis of neurotransmitters such as serotonin (5-HT), and ultimately lead to the onset of depression (Haroon and Miller, 2017; Leonard, 2018). Moreover, higher concentrations of several chemokines, such as CCL2 and CXCL8, were detected in the serum and CSF of depressed patients (Sutcigil et al., 2007; Piletz et al., 2009; Black and Miller, 2015; Khandaker et al., 2015; Slusarczyk et al., 2016). Previous studies have demonstrated that the proliferation of mononuclear cells is suppressed and T cell mitogens in the blood are decreased in patients with severe depression (Nunes et al., 2002; Irwin and Miller, 2007), and that impaired cell-mediated immunity is involved in the pathophysiology of depression (Kohler et al., 2017). Other studies have demonstrated a strong correlation between Th$_{17}$ immune cells and the progression of depression (Korn et al., 2009; Slyepchenko et al., 2016).

As mentioned above, inflammatory responses and immunity are involved in the development and onset of depression (**Figure 2**). Modulation of inflammation may thus mitigate depressive behavior in patients with depression.

GLP-1 has been reported to promote the production of anti-inflammatory cytokines in various organs including the adipose tissue and pancreas, and the brain (Dobrian et al., 2011; Lee et al.,

TABLE 1 | Possible association between glucagon-like peptide 1 (GLP-1) and depression based on previous studies.

| Experiment target | Result | Reference |
|---|---|---|
| GLP-1 or exendin-4 | Influenced the dopamine system and reduced food reward behavior | (Richard et al., 2015) |
| Liraglutide | Exerted antipsychotic effect | (Dixit et al., 2013) |
| Exendin-4 | Reduced cocaine self-administration | (Sorensen et al., 2015) |
| Exendin-4 | Elevated turnover of dopamine through dopamine receptor 2 signaling | (Anderberg et al., 2014) |
| GLP-1R activation | Stimulated the release of GABA, glutamate, serotonin, and dopamine | (Rebosio et al., 2018) |
| Liraglutide or exendin-4 | Enhanced neurogenesis and neural proliferation | (Bertilsson et al., 2008; Li et al., 2009; Isacson et al., 2011; Darsalia et al., 2012; McGovern et al., 2012; Porter et al., 2013; Parthsarathy and Holscher, 2013a; Holscher, 2014; Darsalia et al., 2014b; Sango and Utsunomiya, 2015) |
| (Val(8))GLP-1-Glu-PAL | Increased hippocampal neurogenesis and cell proliferation | (Lennox et al., 2013) |
| P7C3 (aminopropyl carbazole compound) | Activation of cAMP/PKA and Akt/GSK3 signaling | (Wang et al., 2018) |
| Liraglutide | Promoted neurite outgrowth through Wnt signaling | (He et al., 2018) |
| Liraglutide | Enhanced synaptic plasticity and attenuated depressive behavior | (Weina et al., 2018) |
| Liraglutide | Improved cognitive function and depressive symptoms in patients | (Cuomo et al., 2018) |
| Sitagliptin | Enhanced cognitive function and protected neurons against oxidative stress | (Gault et al., 2015) |
| Liraglutide | Activated LTP and improved cognitive dysfunction | (McClean et al., 2011) |
| GLP-1R knockout mouse | Impaired synaptic plasticity and memory formation | (Abbas et al., 2009) |
| GLP-1R overexpression mouse | Enhanced learning and neuroprotection | (During et al., 2003) |
| GLP-1 or exendin-4 | Chronic administration reduced depression-like behavior | (Anderberg et al., 2016) |
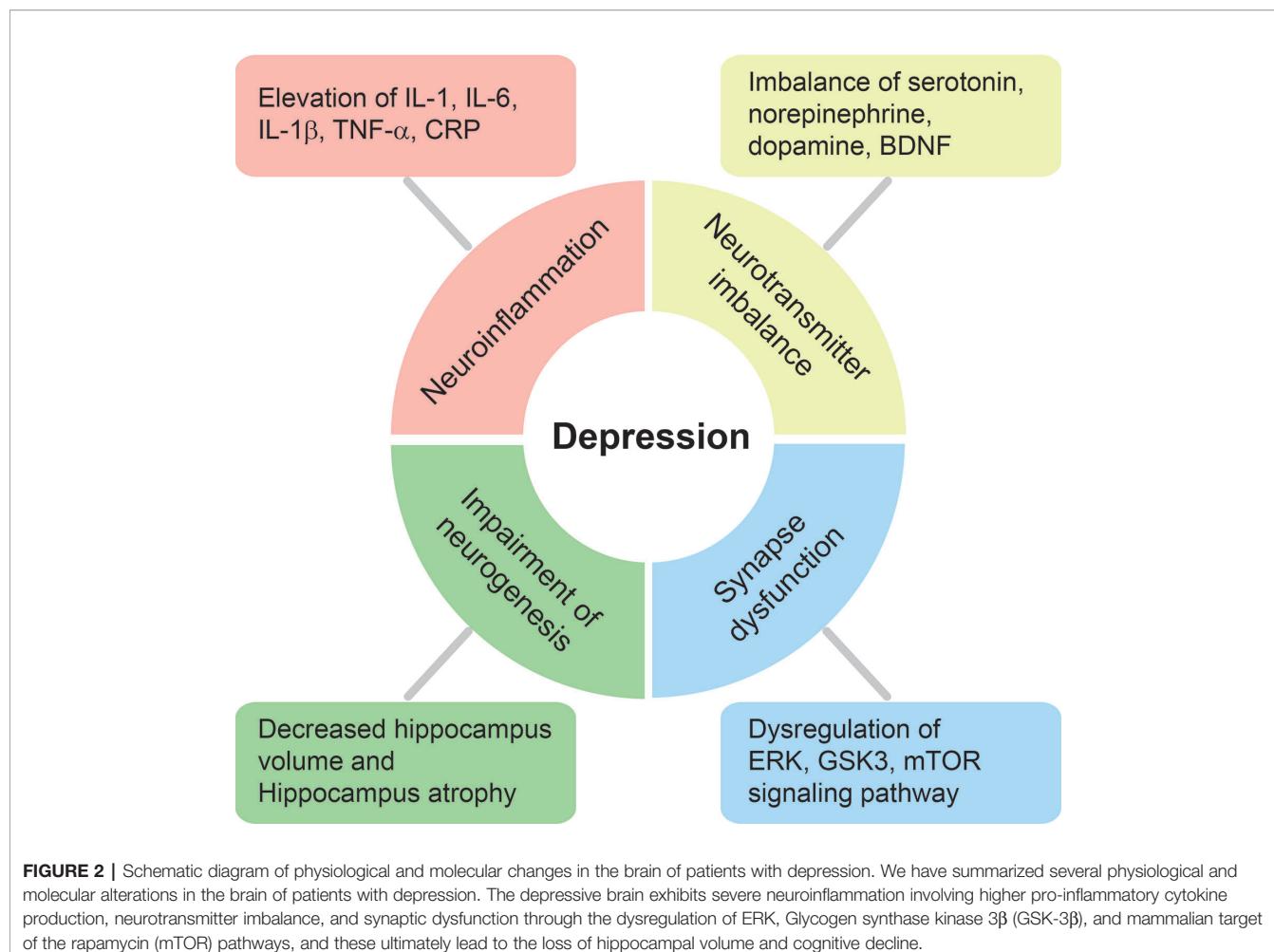
**FIGURE 2 |** Schematic diagram of physiological and molecular changes in the brain of patients with depression. We have summarized several physiological and molecular alterations in the brain of patients with depression. The depressive brain exhibits severe neuroinflammation involving higher pro-inflammatory cytokine production, neurotransmitter imbalance, and synaptic dysfunction through the dysregulation of ERK, Glycogen synthase kinase 3β (GSK-3β), and mammalian target of the rapamycin (mTOR) pathways, and these ultimately lead to the loss of hippocampal volume and cognitive decline.

2012; Darsalia et al., 2014a; Augestad et al., 2020; Reed et al., 2020). In addition, GLP-1 can boost immune cell infiltration as well as the production of pro-inflammatory cytokines under inflammatory conditions (Liu et al., 2009; Parthsarathy and Holscher, 2013b). One study demonstrated that exendin-4 (50 nM) treatment reduces the expression of pro-inflammatory genes such as NF-κB p65 and the TNF receptor superfamily member 1A in human pancreatic islet cells (Velmurugan et al., 2012). In addition, treatment of a DPP-4 inhibitor in diabetic mice increased the levels of anti-inflammatory cytokines, and increased the activation of regulatory T cells, indicating an involvement in the pathology of diabetes (Tian et al., 2010). Another study has reported that treatment of the DPP-4 inhibitor vildagliptin (10 mg/kg) in STZ-induced diabetic rats suppresses plasma TNF-α concentrations and inhibits nitric oxide concentrations in the serum (Akarte et al., 2012). Exendin-4 (10 nM) promotes the expression of serine protease inhibitor-9, thus underlying the survival capability of cells against the attack of immune cells such as natural killer cells and cytotoxic T cells in human islets (Cechin et al., 2012).

In the brain, GLP-1 treatment has a preventive effect on the progression of Alzheimer's disease pathology in rats (Iwai et al., 2014; Solmaz et al., 2015). Exenatide-4 (20 μg/kg/day). GLP-1

treatment suppressed the level of TNF-α in an Alzheimer's disease animal model brain induced by injection of STZ (Solmaz et al., 2015). Additionally, GLP-1 (50 nM) protected against synaptic dysfunction in the rat hippocampus induced by injection of lipopolysaccharide (LPS) (Iwai et al., 2014). In an Alzheimer's disease mouse model, liraglutide (25 nmol/kg/day) treatment attenuated the neuroinflammation response in the cortex (McClean et al., 2011). In addition, the Alzheimer's disease APPSWE/PS1ΔE9 mouse model showed a reduction of neuroinflammation upon liraglutide treatment (Holscher, 2014). Exendin-4 treatment (0.5 μg/kg) resulted in a reduction of pro-inflammatory cytokines such as TNF-α and IL-1β in CSF and in hippocampal and cortical brain areas (Ventorp et al., 2017).

Thus, GLP-1 can improve responses to neuroinflammation, and controls the production of cytokines in the brain. This function of GLP-1 under an inflammatory condition shows the therapeutic possibility of GLP-1 in the depressive brain accompanied by neuroinflammation.

## Neurotransmitter Imbalance in Depression and Its Relation to GLP-1

Neurotransmitters play a cardinal role in the brain and contribute to the regulation of behavior (Lener et al., 2017).

Depression is typically thought to arise from a neurotransmitter imbalance (**Figure 2**) (Lener et al., 2017). Previous studies have demonstrated that the deficiency of monoaminergic neurotransmitters, such as 5-HT, norepinephrine (NE), and dopamine (DA), aggravates depressive behaviors and can be used as a diagnostic index for depression (Massart et al., 2012; Hamon and Blier, 2013). Serotonin is critical for mood processing and emotional regulation in brain areas such as the amygdala and hippocampus (Hervas et al., 2000; McKie et al., 2005), and may be essential for ameliorating depressive behaviors. Clinically depressed patients reportedly have impaired glutamatergic and hyperactive acetylcholine systems, whereas they have a dramatically suppressed gamma-aminobutyric acid (GABA) system (Pytka et al., 2016; Murrough et al., 2017). A previous brain magnetic resonance spectroscopy imaging study demonstrated that the levels of GABA and glutamate cycling was abnormal in patients with depression when compared to those in the normal brain (Sanacora et al., 2008). Yuen et al. demonstrated that chronic stress disrupts glutamate transmission in the PFC and cognition-related brain regions (Yuen et al., 2012). A number of other studies have also suggested that chronic stress causes atrophy of the PFC and hippocampus owing to glucocorticoid imbalance (Eisch and Petrik, 2012; McEwen et al., 2012).

Brain-derived neurotrophic factor (BDNF) is important for neurogenesis, and various depressive symptoms arise from decreased BDNF levels (Sahay and Hen, 2007). A previous study reported that anti-depressant therapy can increase the level of BDNF and subsequently boost neurogenesis, attenuate neuronal apoptosis in the depressive brain, and ultimately improve depressive mood (Sahay and Hen, 2007). Furthermore, recovery of BDNF levels results in the improvement of neuroplasticity and reduction of neuronal apoptosis (Alves et al., 2017; Kraus et al., 2017). Decreased BDNF in the hippocampus and PFC has been noted in depressed patients (Krishnan and Nestler, 2008; Duman and Voleti, 2012). Anti-depressants, which increase BDNF levels, lead to improvements in depressive behavior in BDNF-deletion mutant mice (Taliaz et al., 2010; Duman and Voleti, 2012; Yu et al., 2012). Some studies have reported that depression caused by chronic stress disrupts the BDNF–tropomyosin related kinase B (TrkB) receptor signaling pathway in the PFC and hippocampus, and ultimately contributes to impaired synaptic maturation, synaptic protein synthesis, and glutamate receptor cycling (Collingridge et al., 2010; Duric et al., 2010; Hoeffer and Klann, 2010; Christoffel et al., 2011; Duman and Voleti, 2012).

Therefore, because neurotransmitter imbalance contributes to depressive behaviors in patients with depression as described above, the appropriate modulation of neurotransmitters in the brain is key to treating depression (**Figure 2**).

A previous study reported that GLP-1Rs are observed in brain regions related to energy balance and regulation of moods, such as the amygdala, hippocampus, and dorsal raphe nucleus (Merchenthaler et al., 1999). Some studies have also shown the presence of GLP-1Rs in mood-related brain regions and demonstrated its powerful role in emotional processing within the CNS (Merchenthaler et al., 1999; Sharma et al., 2015).

Serotonin is produced by specific neurons localized in raphe nuclei in the brainstem (Llewellyn-Smith et al., 2013). These neurons innervate the amygdala (Vertes, 1991) and the hippocampus (McQuade and Sharp, 1997). The endogenous ligands of GLP-1-producing neurons were found to innervate the brainstem raphe nuclei (Llewellyn-Smith et al., 2013). Another study reported that injection of the GLP-1 agonist exendin-4 influenced the dopamine system and reduced food-related reward behavior in rats (Hayes and Schmidt, 2016). In patients with depression, the reward learning process is disrupted, and impaired reward learning is thought to lead to depressive mood and behavior (Fletcher and Reback, 2015). Dopamine regulates the reward learning system by stimulating the mesolimbic circle (Steinberg et al., 2013; Lietzau et al., 2020).

The exendin-4 treatment has been shown to reduce cocaine self-administration, suggesting that the GLP-1 system may be a novel target of drug addiction (Sorensen et al., 2015). Dopamine as a neurotransmitter has also been shown to reduce depressive-like behaviors such as anxiety (Dunlop and Nemeroff, 2007; Tye et al., 2013; Mohammadi et al., 2015; Lietzau et al., 2020). Recent studies have demonstrated that the GLP-1 agonist, liraglutide, exerts an antipsychotic effect in a mouse model of psychosis (Dixit et al., 2013). GLP-1 can elevate the turnover of dopamine in the brain amygdala through dopamine receptor 2 signaling (Anderberg et al., 2014; Lietzau et al., 2020). Furthermore, GLP-1Rs have been shown to be able to stimulate the depolarization-evoked release of other neurotransmitters, such as GABA and glutamate, as well as of serotonin and dopamine, in the cortex and hippocampus (Rebosio et al., 2018).

These studies indicate that GLP-1 modulates the release of several neurotransmitters including serotonin, dopamine, GABA, and glutamate, which may regulate depressive-like behaviors. Modulation of neurotransmitter secretion by GLP-1 may be another effective solution for alleviating the effects of depression.

## Neurogenesis in Depression and Its Relation to GLP-1

In the brain, neurogenesis is a critical repair response against stress and age (Dranovsky et al., 2011). New neurons generated through the neurogenesis process are produced from neural progenitors mainly located in the subgranular zone of the dentate gyrus (Dranovsky et al., 2011). Neurogenesis repairs the damaged brain and improves cognition (Schmidt-Hieber et al., 2004). The depressive brain has been shown to exhibit a decrease in hippocampal neurogenesis, and this reduction is recovered by antidepressant drug treatment (Tanti and Belzung, 2013). Some brain imaging studies have demonstrated that depressed patients show neuronal atrophy and decreased volume of the cortex and limbic lobe regions, including the PFC and hippocampus. These regions are known to regulate emotion and cognition, and pathological problems and impaired

cognitive function are observed in depressive conditions (Price and Drevets, 2010; MacQueen and Frodl, 2011).

Patients with recurrent depression exhibit reduced hippocampal volume and hippocampal atrophy in the brain when compared to healthy controls (**Figure 2**) (Bremner et al., 2000). Moreover, the decrease in hippocampal volume is significantly related to the total duration of depressive episodes (Sheline et al., 1999). Other studies have reported that a reduction in hippocampal neurogenesis leads to an increase in anxiety symptoms and the onset of depression (Hanson et al., 2011; Eisch and Petrik, 2012; Moylan et al., 2013; Smitha et al., 2014). Increased hippocampal neurogenesis influences anxiety and depressive behavior through the HPA axis and is considered a promising strategy to promote antidepressant-like effects (Hill et al., 2015).

Calcium signaling resulting from GABA receptor activation has been found to promote neuronal differentiation and control the synaptic integration of neuronal precursor cells (Ge et al., 2006). A serotonin 5-HT$_{2A}$ receptor antagonist was shown to reduce neuronal proliferation, and chronic administration of a 5-HT$_{1A}$ receptor agonist increased neuronal proliferation (Jha et al., 2008). With this perspective, the regulation of neurotransmitter secretion may be considerably linked with the activation of neurogenesis in the depressive brain. Moreover, chemokines are important regulators of neuronal proliferation and neural progenitor cell differentiation (Tran et al., 2007; Miller et al., 2008). As such, cytokine and chemokine dysregulation likely contribute to impaired neurogenesis in the depressive brain. Thus, we expect that the promotion of neurogenesis in the brain may be a key strategy to cure depression.

The GLP-1R agonist exendin-4 was shown to promote neurogenesis in the subventricular zone region in a neurodegenerative disease rodent model (Bertilsson et al., 2008). Interestingly, several studies have demonstrated that exendin-4 has neurotrophic and neuroprotective effects and that it enhances neurogenesis and neural proliferation (Li et al., 2009; Holscher, 2014; Sango and Utsunomiya, 2015). Furthermore, Isacson et al. demonstrated that GLP-1 agonist administration could lead to an increase in neurogenesis in the hippocampus dentate gyrus region, and demonstrated an improvement in mood and cognitive function through the swim test in adult rodents (Isacson et al., 2011). Moreover, GLP-1 has been reported to enhance synaptic plasticity and synaptic formation in the hippocampus (Cai et al., 2014). The increase of hippocampal neurogenesis is essential for improved cognitive function induced by environmental factors such as exercise (Petrik et al., 2012; Klempin et al., 2013).

Previous studies have demonstrated that neurogenesis influences emotional regulation in adult mice (Deng et al., 2009), and that enhanced neurogenesis in the hippocampus acts as an antidepressant for increasing serotonin receptor activity (Wang et al., 2008; David et al., 2009; Kondo et al., 2015). Moreover, hippocampal neurogenesis reduces neuronal damage by replacing lost neurons, which appears to improve depressive-like behavior (Zhang et al., 2008). It has been demonstrated that the administration of GLP-1 analogs,

including liraglutide and exendin-4, promotes neurogenesis and neural progenitor cell proliferation in the hippocampus of rodent models (Darsalia et al., 2012; McGovern et al., 2012; Porter et al., 2013). It has also been reported that liraglutide increases neural stem cell proliferation and neuronal differentiation in the APP/PS1 neurodegenerative disease model (Parthsarathy and Holscher, 2013a). Moreover, a GLP-1 analog, (Val(8))GLP-1-Glu-PAL, increased hippocampal neurogenesis and cell proliferation in obese mice fed a high-fat diet (Lennox et al., 2013). Further, the expression of neurogenesis-related proteins was promoted by the activation of the cAMP/PKA and Akt/GSK3 signaling pathways through the stimulation of GLP-1R in mice (Wang et al., 2018). From *in vitro* studies using human SH-SY5Y neuronal cells, it was demonstrated that cell proliferation is increased with GLP-1 treatment (Li et al., 2010; Salcedo et al., 2012).

Some studies demonstrated that the administration of antidepressants leads to an improvement in depressive mood through the increase of hippocampal neurogenesis and the enhancement of synaptic connectivity (Duman et al., 2001; Toni et al., 2007; Boldrini et al., 2009; Denny et al., 2012). Several studies have demonstrated that increasing neurogenesis in the brain is an effective therapeutic approach for reducing depressive-like behaviors (Anacker et al., 2011; Mendez-David et al., 2013; Weina et al., 2018). A previous study indicated that treatment with the GLP-1 agonist liraglutide (subcutaneously at a dose gradually titrated from 0.6 to 3 mg) in bipolar and mood disorder depression patients could result in an improvement in cognitive function and an alleviation of depressive pathological symptoms (Cuomo et al., 2018).

Considering this evidence, increasing neurogenesis in the brain through the GLP-1 pathway may provide a novel approach for improving depressive-like behavior in patients with depression.

## Synaptic Dysfunction and Memory Loss in Depression and Its Relation to GLP-1

In patients with depression, neural circuits are impaired as a result of aberrant communication between neurons (Williams, 2016). Functional brain imaging studies have reported a decrease in synaptic connectivity and neuronal circuitry in the PFC and hippocampus in depressed patients (Perlman et al., 2012; Zeng et al., 2012). Moreover, postmortem brains of depressed patients are reduced in size and show loss of pyramidal neurons (Rajkowska et al., 1999), GABAergic interneurons, and glia in the PFC (Rajkowska et al., 2007). Several neuronal morphological studies also reported a reduction in synapse number and synaptic signaling proteins in the PFC of depressed patients through electron microscopy (Kang et al., 2012). Reduced glutamate receptors, presynaptic neurotransmitter proteins, and postsynaptic functional proteins in the PFC and hippocampus were also observed (**Figure 2**) (Zhao et al., 2012; Duric et al., 2013).

Chronic unpredictable stress, considered a model of depression, results in a reduction in dendritic lengths and

branching of apical dendrites, the loss of functional synaptic spines, and the reduction of dendritic complexity in PFC neurons and in the hippocampal CA3 pyramidal neuronal cell layer (McEwen et al., 2012; Morrison and Baxter, 2012). Furthermore, chronic stress aggravates neuronal damage in the amygdala and nucleus accumbens and subsequently disrupts the motivation and reward system (Duman and Voleti, 2012). Another study reported that depression caused by chronic stress blocks glutamate signaling and synaptic transmission, and this ultimately leads to cognitive dysfunction (Yuen et al., 2012). Moreover, depressed patients show a reduction in synaptic density proteins in response to stress (Kang et al., 2012). Depression reportedly increases the negative regulation of ERK signaling associated with synaptic plasticity (Duric et al., 2010) and inhibits downstream signaling of BDNF and neuritin that are essential for normal synaptic function (Son et al., 2012).

Glycogen synthase kinase 3 (GSK3) has been shown to regulate synaptic homeostasis in the brain (Collingridge et al., 2010). Many researchers have demonstrated that depressed patients have excessive activation of GSK3-deconsolidation, which leads to a reduction in synaptic spines (Li and Jope, 2010; Wilkinson et al., 2011). Previous studies have shown that synaptic plasticity, synaptic transmission, and long-term potentiation (LTP) are dramatically attenuated in the depressive brain (Karpova et al., 2011; Bath et al., 2012). In dendrites and cell bodies of the neuron, activation of the mammalian target of the rapamycin (mTOR) signaling pathway accelerates long-term synaptogenesis (Hoeffer and Klann, 2010). In the depressive brain, activation of mTOR is reduced, which subsequently decreases the release of BDNF and the synthesis of synaptic proteins (Jourdi et al., 2009).

Most patients with depression show mood disturbances, as well as general cognitive impairment, which may explain the two-fold greater risk of dementia development seen in such patients (Bulbena and Berrios, 1986; Kohler et al., 2010; Byers et al., 2012; Tsai and Rosenheck, 2016). A neuroimaging study suggested that depression strongly leads to memory dysfunction given that morphological changes in the brain of depressed patients, such as atrophy and abnormal alteration of the frontal cortex, thalamus, and hippocampus, is related to cognitive impairment (Zhang et al., 2016).

Based on these reports, the impairment of synaptic function and synaptic transmission and the loss of synaptic density proteins are widely observed in the depressive brain (**Figure 2**). Synaptic dysfunction may lead to memory dysfunction in patients with depression. Therefore, improving synaptic function is an important component for treating depressive neuropathology.

One study reported that GLP-1 is negatively correlated with body mass index (BMI) and that it appears to increase dentate gyrus neurogenesis based on immunostaining images (Coplan et al., 2014). Recent research has demonstrated that liraglutide promotes neurite outgrowth of cortical neurons in severe oxidative stress conditions through Wnt signaling (He et al., 2018). Furthermore, another study has highlighted the role of liraglutide in preventing depressive-like behaviors by enhancing

hippocampal neuron synaptic plasticity (Weina et al., 2018). Gault et al. demonstrated that oral administration of the DPP inhibitor sitagliptin (50 mg/kg) can enhance cognitive function and protects neurons against oxidative stress in high fat-fed mice (Gault et al., 2015). One *in vitro* study reported that exendin-4 increases the number of neurites, promotes neuronal outgrowth, and considerably increases neurite length (Luciani et al., 2010).

It was previously shown that the GLP-1 receptor can control neuronal function in the rat hippocampus by enhancing GABAA signaling through presynaptic and postsynaptic mechanisms (Korol et al., 2015). Previous studies reported that the administration of the GLP-1R agonist exendin-4 (25 nmol/kg, twice daily) inhibits learning and memory formation through the suppression of synaptic plasticity in the hippocampus of a high fat diet mouse model (Gault et al., 2010; Lennox et al., 2014).

LTP results from the synchronous activity of neurons and is widely considered an indicator of memory formation. One study demonstrated that GLP-1 can activate LTP in the brain and ameliorate cognitive dysfunction in a neurodegenerative disorder model (McClean et al., 2011). Another study showed that GLP-1R knockout mice have impaired LTP when compared to control animals (Abbas et al., 2009). Overexpression of GLP-1Rs in the mouse brain leads to enhanced learning, as measured with the Morris water maze and learning performance tests (During et al., 2003). Interestingly, a recent study showed that GLP-1 and exendin-4 induced anxiety-like behaviors in mice (Anderberg et al., 2016). The stimulation of GLP-1Rs alters serotonin signaling in the amygdala (Anderberg et al., 2016). Importantly, chronic administration of exendin-4 significantly reduces depression-like behavior (Anderberg et al., 2016).

These previous studies together suggest that GLP-1 may improve memory and cognitive function in patients with depression by enhancing synaptic function and neuronal signal transmission in the brain.

## CONCLUSIONS

In this review, we have presented four cardinal points about the roles of GLP-1 in the depressive brain. First, we summarized significant evidence pointing to the relationship between neuroinflammation and GLP-1 administration. GLP-1 appears to attenuate the process of neuroinflammation and protects neurons and glia under oxidative stress conditions in the depressive brain. Second, we described the role of GLP-1 in neurotransmitter homeostasis in the depressive brain in which GLP-1 can improve neurotransmitter balance. In the depressive brain, the secretion of diverse neurotransmitters is not stable compared to that in the normal brain. GLP-1 is a useful therapeutic modulator of depression, suggesting that abnormal alteration of neurotransmitter levels in the depressive brain results in mood impairment and cognitive decline. Third, we reviewed the role GLP-1 in promoting neuronal differentiation and neural stem cell proliferation in the depressive brain. GLP-1 is a promising target for the treatment of depression because

impaired neurogenesis ability and the reduction of neuronal differentiation leads to multiple depressive pathological symptoms. Finally, we summarized studies showing that GLP-1 can enhance cognitive decline by improving synaptic function in the depressive brain. GLP-1 ameliorates synaptic dysfunction in the depressive brain and subsequently leads to the enhancement of cognitive function. Hence, GLP-1 may be key to improving cognitive decline in patients with depression.

Taken together, we have highlighted GLP-1 as a novel therapeutic marker for identifying and treating the neuropathology of depression. Furthermore, we emphasize the necessity of further studies concerning the mechanisms and function of GLP-1 in the depressive brain. Similar to the use of GLP-1 analogs in diabetic patients, we believe that GLP-1 may be used for patients with depression in the near future.

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