A New Perspective on Hippocampal Synaptic Plasticity and Post-stroke Depression

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Abstract

Post-stroke depression (PSD), a common complication after stroke, severely affects the recovery and quality of life of patients with stroke. Owing to its complex mechanisms, PSD treatment remains highly challenging. Hippocampal synaptic plasticity is one of the key factors leading to PSD; however, the precise molecular mechanisms remain unclear. Numerous studies have found that neurotrophic factors, protein kinases, and neurotransmitters influence depressive behavior by modulating hippocampal synaptic plasticity. This review further elaborates on the role of hippocampal synaptic plasticity in PSD by summarizing recent research and analyzing possible molecular mechanisms. Evidence for the correlation between hippocampal mechanisms and PSD helps to better understand the pathological process of PSD and improve its treatment.

Introduction

Post-stroke depression (PSD), a common complication after stroke, severely affects the recovery and quality of life of patients with stroke. Owing to its complex mechanisms, PSD treatment remains highly challenging. Hippocampal synaptic plasticity is one of the key factors leading to PSD; however, the precise molecular mechanisms remain unclear. Numerous studies have found that neurotrophic factors, protein kinases, and neurotransmitters influence depressive behavior by modulating hippocampal synaptic plasticity. This review further elaborates on the role of hippocampal synaptic plasticity in PSD by summarizing recent research and analyzing possible molecular mechanisms. Evidence for the correlation between hippocampal mechanisms and PSD helps to better understand the pathological process of PSD and improve its treatment.
Post-stroke depression (PSD), a common neuropsychological disorder with a prevalence of up to one-third of post-stroke complications, has a serious negative impact on the life, psychology, and recovery of patients with stroke (Villa et al. 2018). As its prevalence has increased, numerous clinical trials have identified risk factors for PSD, including age, gender, history of depression, stroke severity, and lesion site (Cheng et al. 2018). However, its pathogenesis and available pharmacological treatments remain unclear. Therefore, the exploration of the pathological mechanisms underlying PSD and the search for effective treatments are of great significance.

Although a large number of mechanisms have been proposed to explain the occurrence of PSD, including abnormalities in the hypothalamus-pituitary-adrenal axis (Farrell et al. 2018), inflammatory response (Ferrucci and Fabbri 2018), monoaminergic hypothesis (van Praag et al. 1973), neurotrophic hypothesis, and altered neuroplasticity (Castren and Monteggia 2021), the specific biological mechanisms remain unclear. Neuroplasticity has received increasing attention in the study of affective disorders-like symptoms. Studies have shown that neuronal apoptosis and synaptic dysfunction in cortical limbic brain regions can induce depression (Chia et al. 2020). The hippocampus, an important cortical limbic brain region for neurogenesis, is the most common brain region used in depression research. Numerous studies have found that the development of depressive disorders is associated with hippocampal neuroplasticity, including changes in the hippocampal structure, neuronal apoptosis, and reduced neurogenesis (Ishikawa et al. 2019). Hippocampal synaptic alterations underlie altered neuronal plasticity. In the central nervous system, synaptic alterations occur because of changes in synaptic morphology and function due to synaptic plasticity, mainly long-term synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) (Kasai et al. 2017). In stress-induced depression-like rats, hippocampal LTP is impaired whereas LTD is facilitated, and this process can be reversed by antidepressant drugs (Liu et al. 2017). In addition, hippocampal volume decreases in mice after stroke, and neurons undergo apoptosis (Amtul et al. 2014; Li et al. 2021). This suggests that hippocampal neuroplasticity plays a key role in post-stroke depressive disorder (Figure 1).

Recent studies have found that brain-derived neurotrophic factor (BDNF) participates in synaptogenesis by modulating different postsynaptic receptors and activating downstream signaling (Missale et al. 1998). Moreover, this modulation has a bidirectional effect on PSD (Wang et al. 2021; Yang et al. 2021). The autophosphorylating Ca\(^{2+}/\text{calmodulin-dependent protein kinase II} (\text{CaMKII})\), an enzyme associated with hippocampal synaptic plasticity, is involved in LTP and LTD processes (Yasuda et al. 2022). In hippocampal astrocytes, the gap-junction protein connexin 43 (Cx43) and its linker protein regulate synaptic activity (Murphy-Royal et al. 2020). In addition, neurotransmitters and their receptors associated with synaptic activity also play a key role in hippocampal processes involved in PSD (Ji et al. 2014). In this article, we discuss the role of these factors in modulating hippocampal synaptic plasticity during PSD. This enables us to better understand the specific molecular mechanisms of altered hippocampal synaptic plasticity in PSD.

**Neurotrophic factors regulate synaptic plasticity**

BDNF is a neurotrophic cytokine that plays an important role in the central nervous system. It not only regulates synaptic plasticity and neuronal development but is also an important factor in the regulation of mood disorders (Wang et al. 2022). Berton et al. found in various animal models of depression that BDNF levels in the nucleus accumbens of depression model rats remained unchanged or even increased (Berton et al. 2006; Dandekar et al. 2019), whereas BDNF levels in the hippocampus decreased (Rahmani et al. 2020; Wang et al. 2023). Pro-BDNF is a BDNF precursor that is cleaved into mature BDNF (Wang et al. 2021). Clinical studies have found that serum levels of BDNF in patients with depression were decreased, whereas pro-BDNF levels were increased (Gelle et al. 2020). Furthermore, in post-stroke patients, BDNF levels were lower in the serum than in patients without depression, and depressive symptoms were alleviated by antidepressant drugs or exogenous BDNF (Zhang and Liao 2020). The mechanism related to mood regulation by BDNF in the hippocampus is mainly accomplished by acting on different receptors to regulate hippocampal synaptic plasticity (Kowianski et al. 2018; Micheli et al. 2018a; Nutt 2008). BDNF can promote LTP induction in the hippocampus in conjunction with the tropomyosin receptor kinase B (TrkB) (Nibuya et al. 1995), and conversely pro-BDNF can promote apoptosis of neuronal cells and inhibit LTP.
occurrence in conjunction with the p75 neurotrophin receptor (p75NTR) (Luo et al. 2019) (Figure 2). This strongly suggests that BDNF in the hippocampus is involved in the onset of depression after stroke by regulating synaptic plasticity.

**BDNF–TrkB promotes LTP**

BDNF in the hippocampus is involved in the physiological and pathological processes of depression by targeting TrkB receptors to regulate LTP (Kozisek et al. 2008; Zhang et al. 2016). A study found lower protein and mRNA levels of BDNF and TrkB in the hippocampus by comparing the brains of people who had died by suicide due to depression with those of people who had died in traffic accidents (Chhibber et al. 2017a; Erbay et al. 2021). Decreased BDNF and TrkB expression in the hippocampus was also found in a mouse model of corticosterone-induced depression, and antidepressant treatment ameliorated this pathological change (Erbay et al. 2021). The treatment of PSD mice with the TrkB antagonist ANA-12 reduced the benefits of antidepressant drugs (Ren et al. 2021). Related studies have reported that both BDNF–TrkB signaling and the corresponding expression levels were attenuated in the hippocampus in a rat model of PSD, and antidepressant drug treatment or other physical treatments stimulated this signaling pathway (Jiang et al. 2021a; Kang et al. 2021). Similarly, in depression induced by hemorrhagic stroke, the BDNF–TrkB pathway plays a key role (Infantino et al. 2022). A recent clinical investigation in China showed that TrkB gene polymorphisms were significantly associated with PSD (Liang et al. 2018; Zhou et al. 2015).

Both BDNF and TrkB are involved in depression by inhibiting LTP in the hippocampus (Graciano et al. 2014). In the synapse, BDNF acts on pre- and postsynaptic TrkB receptors, and the postsynaptic effect is responsible for the strong induction of LTP by BDNF (Graciano et al. 2014). In the hippocampus, BDNF binds to postsynaptic TrkB receptors, leading to TrkB autophosphorylation. This induces phosphorylation of multiple receptors and increases synaptic transmission by activating several intracellular signaling pathways, including Ras–MAPK, PI3K–AKT, and PLC–Ca2+ (Kowianski et al. 2018; Leal et al. 2017). All these pathways can enhance dendritic growth and differentiation of hippocampal neurons and induce neuronal signaling (Graciano et al. 2014; Harward et al. 2016; Yang et al. 2021) (Figure 2). However, BDNF exerts different effects upon TrkB activation. One study found that exogenous BDNF delivery to cultured hippocampal neurons in both acute and gradual modes induced transient and sustained activation of TrkB, respectively, and the two different activation pathways had different effects, with the former enhancing synaptic transmission and the latter promoting LTP (Ji et al. 2010). Despite their different mechanisms of action, both approaches can activate TrkB and are closely related to PSD. High-frequency neuronal stimulation can increase sustained induction of TrkB phosphorylation caused by external BDNF administration (Guo et al. 2018). Thus, increasing the sustained induction of TrkB phosphorylation by BDNF can promote LTP in synaptic plasticity and is an important mechanism involved in the treatment of depression after stroke.

**Pro-BDNF–p75NTR induces LTD**

Another BDNF-related receptor is p75NTR, which can bind BDNF to regulate synaptic plasticity and induce LTD in hippocampal synapses. However, recent studies have revealed that pro-BDNF, a precursor of BDNF, exhibits a high affinity for p75NTR (Hashimoto 2016). In contrast to the facilitatory effects TrkB has on neurons, p75NTR can bind pro-BDNF to induce neuronal apoptosis (Teng et al. 2005). In a recent study, a PSD model was established using oxygen and glucose deprivation and corticosterone treatment (Yang et al. 2021). In this PSD model, the number of apoptotic hippocampal neurons was significantly increased, and these neurons had a significantly lower number of dendritic spines than the control group (Yang et al. 2021). Moreover, both pro-BDNF and p75NTR receptors were upregulated in the PSD model. These results demonstrate that the binding of pro-BDNF to p75NTR promotes neuronal apoptosis and thereby induces PSD. Another study found that antidepressants improved depression-like behavior and decreased pro-BDNF and p75NTR expression in the hippocampus of rats exposed to chronic unpredictable mild stress (CUMS) (Yang et al. 2020; Yu et al. 2020). Aerobic exercise prevented depression-like behavior in PSD rats while promoting BDNF mRNA expression in the ischemic hippocampus and inhibiting pro-BDNF signaling (Luo et al. 2019). Martinowich et al. found that acute stress had no effect on LTD in hippocampal synaptic
plasticity in p75NTR-deficient mice, suggesting that p75NTR can influence emotion-related behaviors by modulating hippocampal LTD (Martinowich et al. 2012). The administration of antibodies directed against pro-BDNF in the hippocampus was found to be effective in improving depression-like behavior in rats (Zhong et al. 2018). Interestingly, the mechanism of p75NTR action on hippocampal LTD is different in the hippocampus of adult and juvenile rats (Martinowich et al. 2012) as these effects are more pronounced in juvenile hippocampi (Yang et al. 2009). This indicates that the mechanism of pro-BDNF–p75NTR signaling in neuronal synapses in the hippocampus is age-dependent. Many studies have demonstrated that pro-BDNF interacts with p75NTR to induce neuronal apoptosis, leading to a reduction in the number of neurons, which induces the onset of PSD (Koshimizu et al. 2009; Luo et al. 2019; Yang et al. 2014). Therefore, the imbalance between BDNF–p75NTR and BDNF–TrkB signaling pathways causes apoptosis of hippocampal neurons and affects synaptic regeneration, which may be an important mechanism of PSD pathogenesis.

**NMDA receptors regulate hippocampal synaptic plasticity**

LTP and LTD are the main processes involved in hippocampal neuronal synaptic plasticity. Both LTP and LTD cannot be activated without N-methyl-D-aspartate (NMDA)-type receptor (NMDAR) channels (Hammond et al. 1994). However, different subtypes of NMDARs may be involved in different forms of hippocampal synaptic plasticity. Studies have shown that pro-BDNF–p75NTR signaling enhances NMDAR-related subunit NR2B-dependent LTD, as well as their mediated synaptic currents (Bartlett et al. 2007; Woo et al. 2005). Another NMDAR subunit isoform, NR2A, is not only involved in LTP development but also plays a role in LTD induction (Abarzua et al. 2019; Philpot et al. 2007). Pharmacological treatment was found to improve neurological deficits and depressive symptoms by modulating NMDAR channels via BDNF–TrkB signaling in a PSD rat model (Zhao et al. 2021). In a recent clinical trial, serum positivity for NMDAR1-antibodies in patients with acute ischemic stroke was associated with neuropsychiatric symptoms (Deutsch et al. 2021). A related study found that NMDAR upregulation decreases the levels of the synaptic structure-related marker PSD-95, as well as other synaptic proteins associated with synaptic transmission (Wang et al. 2022). These studies provide ample evidence of the regulatory role of BDNF-related receptors in synaptic plasticity which play an important role in the onset and development of PSD.

**Participation of CREB in PSD**

The cAMP response element-binding protein (CREB) is both a BDNF-associated target and a transcription factor that regulates BDNF. It plays a regulatory role in the development of PSD. CREB signaling was diminished in the hippocampus of PSD rats, whereas the administration of antidepressant drugs increased CREB signaling activity and improved depression-like behavior in PSD rats (Jiang et al. 2021b). The expression of molecules involved in the hippocampal neuroplasticity of mice is upregulated shortly after treatment with antidepressants (Sun et al. 2021). This occurs mainly through the activation of BDNF–TrkB signaling to induce CREB phosphorylation (Odaira et al. 2019). This suggests that CREB can act as a downstream target of BDNF–TrkB in the development of PSD. Furthermore, CREB-mediated gene transcription is also extensive. CREB regulates BDNF transcription in the hippocampus through Ser133 phosphorylation thereby regulating its activity and participation in LTP induction (Amidfar et al. 2020). In a study of mice exposed to chronic unpredictable mild stress (CUMS), reduced hippocampal CREB phosphorylation and BDNF protein expression and impaired CREB-BDNF signaling were observed in these mice (Tan et al. 2022). Other studies found that hippocampal CREB phosphorylation is inhibited under chronic stress (Huang et al. 2019) and that with the inhibition of CREB phosphorylation, extracellular signal-regulated kinase (ERK) activity is also reduced (Qi et al. 2008; Wang et al. 2018). In mice treated with antidepressants, ERK signaling increases the expression levels of BDNF and phosphorylated CREB (Sun et al. 2021; Yao et al. 2022), suggesting a regulatory role for CREB–BDNF in depression. In conclusion, the occurrence of PSD is closely related to hippocampal BDNF and CREB expression and is mainly achieved by regulating BDNF–CREB-related signaling.

Based on the knowledge regarding the role of BDNF in the hippocampus and its related targets in PSD, we can conclude that the occurrence and development of PSD are closely related to altered hippocampal synaptic plasticity induced by BDNF and its related signaling in the hippocampus.
CaMKII in the hippocampus regulates PSD

CaMKII regulates synaptic plasticity

The group of CaMks, kinases activated by Ca2+ and calmodulin (CaM), mainly includes CaMKI, CaMKII, CaMKIII, and CaMKIV (Zhang et al. 2021). Among them, CaMKII (mainly CaMKIIα and CaMKIIβ) is expressed at the highest level in the brain, especially in the hippocampus, and has been for many years a key area of research on neuropsychiatric disorders (Shen et al. 2022). The role of CaMKII in neuronal plasticity is structurally accomplished through the structural domain of kinases containing phosphorylation sites and the central structural domain (Robison 2014). At the synapse, including the pre- and postsynaptic membranes, autophosphorylated CaMKII can regulate a variety of protein activities, which further affect the regulation of synaptic plasticity (Salaciak et al. 2021), including LTP and LTD.

CaMKII is involved in synaptic plasticity through its phosphorylation, followed by its interaction with postsynaptic glutamate-related receptors. First, in the excitatory synapses of hippocampal neurons, glutamatergic LTP stimulation allows Ca2+ entry into neurons through GluN2B-containing NMDARs to promote binding of Ca2+ with CaM which then activates CaMKIIα (Lisman 2017) through phosphorylation of Thr286. Subsequently, CaMKIIα acts on NMDAR (mainly GluN2B)-associated protein synthesis (Lisman et al. 2012; Shioda and Fukunaga 2017) and induces LTP in excitatory synapses. Second, phosphorylated CaMKII is transferred to the postsynaptic density and phosphorylates the AMPA receptor (AMPA) glutamate receptor 1 (GluA1) at Ser831 and increases its number, leading to an increase in postsynaptic currents (Lisman et al. 2012). Both pathways suggest that CaMKII Thr286 phosphorylation can maintain LTP by acting on postsynaptic receptors and related proteins. Finally, CaMKII was found to regulate synaptic plasticity through autophosphorylation and Ca2+-dependent phosphorylation in addition to its involvement in the release of neuropeptides and neuromodulators from dense core vesicles in axons and dendrites (Moro et al. 2020). In addition to maintaining and promoting LTP, CaMKII Thr286 phosphorylation can inhibit synaptogenesis and participate in LTD, a process that cannot be separated from the phosphorylation of Ser567, another locus of the glutamate receptor GluA1 (Coultrap et al. 2014).

CaMKII can engage LTP in postsynaptic hippocampal neurons following excitatory stimulation due to Ca2+ influx, but the translocation of phosphorylated CaMKII from the cytoplasm to postsynaptic densities differs depending on the level of excitatory conditions (Tao-Cheng 2020). By modulating CaMKII autophosphorylation in the mouse hippocampus with high- and low-frequency electrical stimulation, Mayford et al. found that different forms of synaptic plasticity can be induced (Mayford et al. 1995). These differences were attributed to different protein kinases activated by CaMKII-dependent phosphorylation (Coultrap and Bayer 2014). Thus, CaMKII phosphorylation acts at different sites in the postsynaptic membrane, inducing the corresponding forms of synaptic plasticity.

CaMKII is involved in LTP

In the postsynaptic density, the autophosphorylated CaMKII Thr286 interacts with multiple proteins involved in LTP (Liu et al. 2020). Zhong, L et al. found that neurogranule protein (Ng) could regulate synaptic CaM localization and promote CaMKII activation to regulate synaptic plasticity. (Zhong and Gerges 2019). The amyloid β peptide may be involved in LTP inhibition by preventing autophosphorylation at CaMKII Thr286, which reduces synaptic transmission, leading to the loss of dendritic spines involved in LTP (Opazo et al. 2018). These experiments confirm that autophosphorylation of CaMKII Thr286 at the synapse may be involved in LTP. Moreover, CaMKII Thr286 autophosphorylation promotes binding to GluN2B-associated proteins to maintain LTP. These proteins include α-actinin, synaptic Ras GTPase activating protein b (SynGAPb), and synapse-associated protein 97 (SAP97). Interference with CaMKII binding to these proteins can reduce synaptic strength (Sanhueza et al. 2011). Compared to wild-type mice, depression-like behavior is reduced in mice lacking GluN2B, suggesting that GluN2B is involved in promoting depression-like behavior (Miller et al. 2014). During LTP, CaMKII/GluN2B mediation was inhibited by the CaMKII inhibitor tatCN21, and synaptic strength was impaired at high inhibitor concentrations, whereas synaptic strength was unchanged at concentrations that inhibited CaMKII activity (Barcomb et al. 2016). This suggests that
CaMKII/GluN2B interactions maintain synaptic strength. AMPARs, another type of glutamate receptor closely related to CaMKII, are also involved in LTP. The antidepressant tianeptine could effectively restore corticosterone-induced inhibition of LTP and reduce depressive behavior in mice by reducing the diffusion of AMPARs via the CaMKII–CACNG2–PSD-95 pathway (Zhang et al. 2013). Enhanced CaMKIIz-mediated AMPAR synaptic transmission alleviated chronic stress-induced depression-like behavior in CUMS mice (Ma et al. 2021). Another study found that enhancement of the CaMKIB-mediated GluA1 pathway in the hippocampus contributes to the recovery of stress-induced depression-like behaviors (Sakai et al. 2021). These results suggest that CaMKII-mediated glutamate receptors in the hippocampus are involved in LTP and regulate depressive behavior.

CaMKII regulates LTD-related mechanisms

CaMKII not only regulates LTP but also participates in the development of LTD by acting on GluA1 Ser567 (Coultrap et al. 2014). Tao et al. found that CaMKII expression was upregulated in the hippocampus of PSD rats and that the CaMKII inhibitor KN93 improved depressive behavior in PSD (Tao et al. 2019). By studying the antidepressant effects of two cyclic enol ether terpene compounds, Zhang et al. found that combined treatment with both compounds rapidly inhibited CaMKII phosphorylation and enhanced BDNF signaling, whereas injection of a CaMKII activator attenuated its antidepressant effects and BDNF expression (Zhang et al. 2022). Similarly, CaMKII was significantly upregulated in the hippocampal CA1 region of rats with depressive behavior (Song et al. 2018), suggesting that CaMKII mediates the LTD-promoting role in depression-related disorders. In the brain, the lateral habenula is a key region in depression-related disorders (Yang et al. 2018). CaMKII and AMPAR activity increased in the lateral rein nucleus in animal models of depression and decreased significantly after antidepressant treatment, an experiment that demonstrated that CaMKII–AMPAR is a key signaling pathway in the lateral rein nucleus regulating depression (Li et al. 2017; Li et al. 2013). CaMKII plays a similar role in the hippocampus. CaMKII is involved in the P2X2-mediated synaptic inhibition of AMPARs (Pougnet et al. 2016). CaMKII inhibitors blocked (RS)-3,5-dihydroxyphenylglycine (DHPG)-induced hippocampal LTD protein synthesis in hippocampal slices, indicating that CaMKII is an important mediator involved in the induction of protein synthesis-dependent LTD.

These findings suggest that CaMKII is involved in the regulation of synaptic plasticity signified by LTP and LTD (Figure 3).

Cx43 and gap junctions in the hippocampus

Astrocytic Cx43 is involved in regulating depression-like behavior

Astrocytes utilize gap-junction proteins such as Cx43 and Cx30 to modulate synaptic transmission within the brain (Giaume et al. 2010; Santello et al. 2019a). Studies have revealed that Cx43-deficient mice, in which the Cx43 protein is removed from astrocytes, exhibit reduced neuronal excitability, impaired synaptic transmission, and reduced synaptic plasticity (Hosli et al. 2022). In a related study, downregulation of the Cx43 gene, which encodes the linker protein Cx43, was observed in hippocampal astrocytes of depressed and suicidal patients, providing genetic evidence for the involvement of Cx43 in depression (Nagy et al. 2017). Cx43 enhances the survival of newly generated neurons in the adult hippocampus (Liebmann et al. 2013). Huang et al. discovered that overexpression of Cx30 and inhibition of Cx43 in the prefrontal cortex and hippocampus of mice experiencing chronic social defeat stress led to increased and decreased neuronal activity, respectively, and affected depression-like behavior (Huang et al. 2019a). These results indicate that Cx43 plays a role in regulating depressive symptoms through the promotion of hippocampal neuronal activity. However, a recent study reported that Cx43 deficiency leads to an increase in antidepressant behavior (Quesseveur et al. 2015). The antidepressant fluoxetine had stronger effects in a mouse model of depression when administered after Cx43 inactivation compared to its administration without Cx43 inactivation. Additionally, a single administration of the Cx43 gap-junction inhibitor carbenoxolone enhanced the antidepressant effects of fluoxetine (Portal et al. 2020). This indicates that Cx43 and its gap-junction channels may be involved in the development of depressive behavior.

Cx43 gap-junction channels regulate hippocampal neuronal plasticity
Lou et al. discovered that the antidepressant ginsenoside induces abnormal gap-junction connectivity between hippocampal astrocytes in rats exposed to corticosterone-induced stress. Additionally, they found that ginsenosides can reverse the decrease in cx43 expression. Furthermore, the effect of ginsenosides is blocked by the administration of the gap-junction blocker carbenoxolone (Lou et al. 2020; Lou et al. 2020; Wang et al. 2021). These studies indicate that the Cx43 gap-junction protein and its pathway in the hippocampus can effectively alleviate depressive behavior induced by CUMS. Similarly, a decrease in Cx43 protein expression was observed in PSD rats (Tao et al. 2019). Hippocampal Cx43 gap junctions play a considerable role in depression. This is achieved through their involvement in regulating neuronal plasticity in the hippocampus by allowing the movement of ions, neurotransmitters, and neuroactive molecules (Chever et al. 2016; Dallerac et al. 2013; Perea et al. 2009). This regulation is dual in nature (Pannasch and Rouach 2013; Rouach et al. 2008). In addition to their direct role in mediating synaptic plasticity, Cx43 gap junctions can regulate other mechanisms. These gap junctions mediate neuronal regulation of intracellular Ca2+ levels and the release of neurotrophic factors in response to glutamate (Chen et al. 2014a; Quesseveur et al. 2013).

Recently, xiaoyao powder was found to function as an antidepressant in a rat model of CUMS-induced depression. It alleviated neuronal damage in the rat hippocampus by upregulating Cx43 and modulating the Cx43 pathway, which is linked to the gap-junction channel in Cx43 (Zhang et al. 2022). In rats with depression-like behavior induced by CUMS, CUMS exposure leads to the production of proinflammatory factors. However, Ginsenoside Rg1 alleviated this behavior and acted as an antidepressant. This effect is achieved by inhibiting the ubiquitinated degradation of Cx43, which in turn improves neuroinflammation (Wang et al. 2021). Therefore, the involvement of Cx43 gap-junction channels in the onset of depression is related to the regulation of neurotrophic factors and neuroinflammation.

**Cx43 gap-junction channels regulate synaptic activity**

Glutamate is the primary neurotransmitter of neuronal activity. Within the hippocampus, Cx43 regulates glutamatergic synaptic transmission and excitatory neurogenesis, primarily by modulating the level of glutamate released from presynaptic glutamatergic vesicle pools (Chever et al. 2014). This indicates changes in AMPARs and NMDARs, as well as synaptic glutamate concentrations, without affecting postsynaptic transmission. Glutamate release from astrocytes influences the release of presynaptic neurotransmitters, which is dependent on the regulation of intracellular calcium ions through astrocytic gap junctions (Huang et al. 2019b). Likewise, the activity of glutamatergic synapses that rely on sodium ions is regulated by Cx43 protein channels. Elevated sodium ion levels within cells can promote sodium-potassium ATPase activity, leading to increased ATP conversion to lactate and ultimately neurogenesis (Langer et al. 2012). Thus, sodium propagation plays a crucial role in the involvement of Cx43 gap-junction proteins in neuronal synaptic plasticity.

Activation of postsynaptic AMPARs and NMDARs through glutamate release across the synaptic gap causes an efflux of potassium ions (Sibille et al. 2014), which leads to cortical spreading depression (Dreier 2011). Astrocytes can enhance the occurrence of LTP in synapses by absorbing potassium ions. The complex structure comprising astrocytes and synapses is referred to as a tripartite synapse (Arizono et al. 2020). Cx43 gap-junction coupling can reduce the activation of extrasynaptically induced LTD by absorbing potassium ions and glutamate synaptically released through NMDARs. This enhances LTP in these synapses (Chever et al. 2014). Overexpression of the linker protein Cx43 can reduce astrocyte volume, increase glutamate and potassium ion spillover, and inhibit LTP (Pannasch et al. 2011). The beneficial effects of caloric restriction on the brain involve decreased Cx43 expression and reduced extracellular glutamate spillover via gap-junction uncoupling, which significantly enhances synaptic LTP (Popov et al. 2020). This implies that the Cx43 gap-junction protein has a dual role in synaptic plasticity, promoting either LTD or LTP. Previous studies have also found that the absence of gap-junction proteins can prevent the redistribution of absorbed glutamate and potassium ions in astrocyte networks, leading to an increase in extracellular glutamate and potassium ions and inducing spreading depression (Sykova et al. 1999). Therefore, we hypothesized that the alteration of extracellular volume in astrocytes through modulation of Cx43 gap-junction coupling may regulate synaptic plasticity.
Astrocytes connected via Cx43 gap junctions play a crucial role in promoting neuronal coordination (Chever et al. 2016). In adult mice, disruption of astrocyte coupling affects hippocampal neuronal excitability and LTP, primarily because of changes in the astrocyte network structure (Hösl et al. 2022; Medina et al. 2016). The impact of astrocyte networks on synaptic neuronal activity has been extensively reviewed by Pannasch et al. (Pannasch and Rouach 2013) and is not discussed further here. In summary, Cx43 gap junctions are involved in regulating synaptic plasticity and thus participate in the modulation of depressive behavior by controlling energy metabolites during synaptic activity, glutamate release, sodium propagation, and potassium spillover. The astrocyte network formed by gap-junction coupling also contributes to this effect (Figure 4).

**Neurotransmitter release from Cx43 hemichannels**

In addition to gap-junction channels, Cx43 functions as a hemichannel, which facilitates communication within cells and may contribute to neuronal synaptic excitability (Abudara et al. 2018). Jeanson et al. investigated the effects of seven classes of antidepressants on astrocytes exposed to lipopolysaccharide (LPS). Their results indicated that antidepressant treatment inhibited hemichannel activity without affecting Cx43 protein expression in astrocytes. However, the effect of gap-junction communication remains unclear (Jeanson et al. 2015). Various explanations are possible for these findings, including the idea that Cx43 hemichannels are only involved in glutamatergic neurotransmission in the LPS model (Orellana et al. 2015a) or that antidepressant drugs reduce proinflammatory cytokines to control hemichannel activity (Chen et al. 2014b). Both hypotheses suggest that inhibition of Cx43 hemichannel activity may be a key mechanism by which antidepressants exert their effects (Abudara et al. 2018).

Astrocytes play a vital role in regulating hippocampal plasticity by controlling the release of D-serine through Cx43 hemichannels (Santello et al. 2019b). The release of D-serine induces synaptic LTP in hippocampal neurons through NMDARs (Yang et al. 2003). However, excessive neurotransmitter release can have detrimental effects on neurons. For instance, neurotoxic perfluorooctane sulphonate can damage hippocampal neurons through the astrocytic Cx43 hemichannel-mediated D-serine/NMDAR signaling pathway, which can be attenuated by glial cell uptake of D-serine inhibitors (Wang et al. 2019). Similarly, the neurotransmitter ATP, released by astrocytes, is crucial for the energy supply in the brain and plays a crucial role in regulating neuronal synapses (Winkler et al. 2017). Moreover, the opening of Cx43 hemichannels can lead to the release of large amounts of glutamate, resulting in an increase in calcium levels and ultimately neuronal excitotoxicity (Chavez et al. 2019). Recent research demonstrated that the opening of Cx43 and PanX1 hemichannels in the hippocampus results in the release of glutamate and ATP, leading to acute or chronic fasciculation stress in rats (Orellana et al. 2015b). These findings indicate that increased Cx43 hemichannels are implicated in the pathogenesis of depression by inducing neuronal damage, primarily through the release of neurotransmitters. In summary, the regulatory functions of astrocytes are essential for maintaining neuronal health and plasticity. Although neurotransmitter release is a critical part of this function, excessive release can lead to detrimental effects on neurons. The opening of Cx43 hemichannels has been implicated in the pathogenesis of depression through its effects on neurotransmitter release and subsequent neuronal damage.

**Serotonin (5-HT) and its receptors**

The neurotransmitter 5-HT is involved in depression

In the hippocampus, 5-HT acts as a neurotransmitter and is involved in regulating synaptic plasticity and neurogenesis (Micheli et al. 2018b; Palacios-Filardo and Mellor 2019). Aerobic exercise can improve depression-like behavior in PSD by upregulating 5-HT levels (Tang et al. 2022). Another study also found that both diosgenin and agomelatine exert their antidepressant effects by increasing 5-HT levels in the hippocampus of rats (Daszuta et al. 2005; Yang et al. 2017). The growth-associated protein GAP-43 enhances neurotransmitter release and neo-synaptic formation, thereby promoting hippocampal synaptic plasticity (Grasselli and Strata 2013). Resveratrol reduces 5-HT reuptake, increases 5-HT transmission, and elevates GAP-43 expression in the hippocampus, resulting in improved depressive behavior in mice (Shen et al. 2020). This suggests that 5-HT-dependent neurotransmission can modulate hippocampal synaptic plasticity and
promote hippocampal neuronal activity to improve depressive behavior. Tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme for 5-HT synthesis, has been found to increase depressive behavior in Tph2 knockout mice, whereas deletion of this synthase impairs synaptic plasticity and LTP in the hippocampus (Gebhardt et al. 2019; Jacobsen et al. 2012). These findings suggest that 5-HT deficiency may induce depressive behavior or by inhibiting hippocampal LTP. However, a separate study found that neuroplastin 65 (Np65) knockout mice exhibited reduced depression-like behavior, reduced 5-HT levels, and increased the number of neurons (Li et al. 2019).

To investigate the role of 5-HT neurotransmitters in hippocampal synapses and their relationship with depressive behavior, a clinical study was conducted on patients with PSD to compare the effects of asparagine and fluoxetine hydrochloride treatment. The results showed that antidepressant treatment significantly increased 5-HT and BDNF levels and improved depressive symptoms (Liang et al. 2019). In addition, LPS stress induced a decrease in 5-HT and BDNF levels in the hippocampus of mice, resulting in severer depressive behavior than that induced by CUMS (Zhao et al. 2019). These findings suggest that these drugs increase 5-HT and BDNF levels to exert their effects and that 5-HT may exert its antidepressant effects by modulating BDNF-related signaling cascades. Overall, the different effects of 5-HT on synaptic plasticity play a critical role in modulating mood. 5-HT neurotransmitters affect the action potential frequency of pyramidal neurons in the hippocampus and modulate GABAergic neurotransmission (Dale et al. 2016; Homan et al. 2015). They can also enhance postsynaptic NDMAR activation, promote LTP expression, or inhibit potassium channels (Palacios-Filardo and Mellor 2019).

5-HT receptors regulate hippocampal neurons

Hippocampal 5-HT receptors regulate synaptic transmission

In the hippocampus, different types of 5-HT receptors play distinct roles in depressive behavior (Figure 5) (Bombardi et al. 2021). First, highly expressed 5-HT1A receptors (5-HT1ARs) are believed to be associated with the onset of depression (Stiedl et al. 2015). Studies have shown that 5-HT1AR antagonists (NAN-90, pindolol, and WAY100635) can block the effects of antidepressants such as adenosine (Kaster et al. 2005), suggesting that the downregulation of 5-HT1ARs in the hippocampus is critical for the induction of depression. In a mouse model of cerebral ischemia, a 5-HT1AR agonist reduced depressive behavior in mice and promoted dendritic remodeling in the hippocampus (Aguiar et al. 2020). This finding indicates that 5-HT1ARs play an important role in PSD. Yu et al. found that Shuyu capsules exert their antidepressant effects by increasing 5-HT1AR protein levels and activating the 5-HT1AR-mediated cAMP–PKA–CREB signaling pathway in the hippocampus (Yu et al. 2021). Similarly, another study found that 5-HT1AR mediates PKA–CREB–BDNF signaling in the hippocampus (Shimizu et al. 2019). Electroacupuncture has been found to reduce 5-HT1A protein expression in the CA1 region of the hippocampus, enhance LTP, and improve depression-like behavior (Chen et al. 2020; Han et al. 2018). Thus, it can be argued that 5-HT1AR-mediated signaling promotes hippocampal LTP as an important mechanism of action of antidepressant drugs to improve depressive behavior. In contrast, 5-HT4 receptor-mediated activation in the hippocampus enhances excitatory transmission at hippocampal synapses (Teixeira et al. 2018), participates in hippocampal neurogenesis, and increases neuronal activity. Furthermore, 5-HT4R agonists decrease burst stimulus-induced LTP, whereas selective 5-HT4R antagonists block this effect (Leceufl et al. 2021). By stimulating adenylate cyclase to elevate intracellular cAMP levels and increase neuronal activity, 5-HT4R exerts its antidepressant effects by modulating synaptic plasticity and increasing hippocampal neurogenesis (Hannon and Hoyer 2008). These findings demonstrate that modulation of synaptic plasticity and promotion of hippocampal neurogenesis through 5-HT4R has an antidepressant effect.

Hippocampal 5-HT receptors promote depressive behavior

As 5-HT receptors in the hippocampus can facilitate neural activity, they can also induce depressive behavior by inhibiting neural activity. A study examining the effects of estrogen on depression revealed that downregulation of BDNF-TrkB signaling in the hippocampus of mice in a depression model induced an increase in 5-HT2A receptor activity and increased their susceptibility to depression (Chhibber et al. 2017b).
This suggests that 5-HT2A plays a facilitatory role in depression, which is regulated by BDNF signaling. The overactivity of another receptor subtype, 5-HT2CR, also contributes to the development of depression. Inhibiting 5-HT2CR-mediated activity of dopaminergic (DA) neurons can reduce the unwanted effects of selective serotonin reuptake inhibitors (SSRIs), such as dyskinesia, whereas 5-HT2C receptor antagonists can enhance the antidepressant and anxiolytic effects of SSRIs and reverse SSRI-mediated motor deficits (Demireva et al. 2020). Similarly, 5-HT7R antagonists have been found to exhibit antidepressant effects (Canale et al. 2016; Kim et al. 2014). Although previous studies have identified a role for 5-HT7R in ameliorating psychiatric disorders (Costa et al. 2012), recent studies have identified 5-HT7R–MMP-9 signaling as a key pathway for inducing depression in the hippocampal CA1 region (Bijata et al. 2022). Overall, studies on 5-HTR have demonstrated its involvement in hippocampal neurogenesis and its differential regulation of depressive behavior. The heteroreceptor complex of 5-HTR also plays an important role in mood regulation. For further details, please see (Borroto-Escuela et al. 2021).

Dopamine and its receptors

Dopaminergic neurons are involved in depression-related emotions

Selegiline is a monoamine oxidase (MAO) inhibitor that improves depressive behavior and has antidepressant effects in patients with Parkinson’s disease (Kasai et al. 2017). The drug enhances hippocampal dopaminergic neurotransmission and reduces hippocampal LTP impairment leading to antidepressant effects, independent of MAO-A inhibition (Ishikawa et al. 2019). These findings suggest that dopaminergic neurotransmission in the hippocampus plays a key role in regulating hippocampal synaptic plasticity independent of 5-HTergic and noradrenergic pathways. MPTP and 6-OHDA are commonly used to induce depression and anxiety in Parkinson’s disease mice with affective disorders (Chia et al. 2020). Increased levels of α-synuclein in the hippocampus of 6-OHDA-treated mice interfered with dopamine release at synapses, leading to the impairment of hippocampal plasticity and neurogenesis, resulting in depression (Schlachetzki et al. 2016). Using a PSD rat model, Chen et al. found that astragaloside VI can reverse the decrease in DA levels in the rat hippocampus and exert antidepressant effects (Chen et al. 2022). The use of antidepressants such as fluoxetine, acetylcholine, and pioglitazone can reverse hippocampal neural damage, counteract dopaminergic neuron-induced apoptosis of neurons in various brain regions, and exert antidepressant effects (Bonato et al. 2018; Dall’e et al. 2020; Singh et al. 2017). Thus, similar to the 5-HT system, the dopaminergic system is involved in depression-like behavior by modulating hippocampal neurogenesis (Mallet et al. 2019). Overall, the antidepressant effects of selegiline may be attributed to its ability to enhance dopaminergic neurotransmission in the hippocampus and reduce hippocampal LTP impairment independent of its MAO-A inhibition. The dopaminergic system plays a crucial role in regulating hippocampal synaptic plasticity and depression-like behavior, and DR agonists may have potential as novel antidepressant agents.

Dopamine receptors mediate hippocampal synaptic plasticity

DRs are composed of five distinct G protein-coupled receptors, which are further divided into D1-like (D1R and D5R) and D2-like (D2R, D3R, and D4R) subfamilies. These receptor classes differently mediate hippocampal synaptic plasticity (Figure 5) (Missale et al. 1998). Modafinil is a novel antidepressant that inhibits excessive autophagy and neuronal cell death in the hippocampus, thereby affecting synaptic transmission (Cao et al. 2019). In a mouse model of menopause, D1R and D2R were found to be involved in the antidepressant effects of modafinil. Furthermore, D1R and D2R antagonists were found to have opposing effects on modafinil-induced neurogenesis in the hippocampus, with the former decreasing and the latter increasing neurogenesis (Yan et al. 2021). D1R agonists enhance the expression and maintenance of LTP in the hippocampal CA1 region, whereas D1R antagonists inhibit it (Huang and Kandel 1995). In contrast, in the dentate gyrus, deletion of the postsynaptic D2R gene together with D2R pharmacological blockade impaired NMDAR-mediated LTP and LTD in the hippocampal CA1 region, whereas its presynaptic deletion had no effect on LTP (Rocchetti et al. 2015). These study findings illustrate the distinct roles of D1- and D2-like receptors in hippocampal synaptic plasticity.

Various hypotheses have been proposed regarding the distinct roles of D1- and D2-like receptors in hippo-
campal synaptic plasticity. First, D1- and D2-like receptors are differentially distributed in the hippocampus. D1-like receptor-mediated signaling occurs primarily in granule cells of the dentate gyrus, whereas D2-like receptor are mainly expressed in hilar mossy cells or the luminal molecular layer of the dorsal hippocampus (Charuchinda et al. 1987; Wei et al. 2018). Furthermore, D1-like receptors positively regulate adenylate cyclase activity, which leads to increased intracellular cAMP levels. Conversely, D2-like receptors negatively regulate adenylate cyclase and decrease intracellular cAMP levels (Klein et al. 2019). Activation of the D4R subtype, a D2-like receptor, reduces synaptically enhanced AMPAR currents and CaMKII activity in the hippocampus. Blocking D4R promotes late hippocampal LTP, which is associated with D2-like receptor regulation by adenylyl cyclase (Navakkode et al. 2017). In contrast, the D3R subtype promotes PI3K- and MEK-induced structural plasticity of DA neurons, which are involved in the antidepressant effects of ketamine (Cavalleri et al. 2018). Therefore, different subtypes of D2-like receptors have different modulatory effects on neurons. Finally, different forms of dopaminergic discharge play a role in the modulation of these receptors. Tonic firing under low-frequency stimulation can only activate D2-like receptors with relatively high affinity, whereas phasic firing under high-frequency stimulation can transiently activate D1-like receptors with low affinity (Edelmann and Lessmann 2018). Activation of D1-like receptors has been found to promote enhanced synaptic glutamatergic transmission of LTP in the CA1 region of the rat hippocampus (Li et al. 2003). In conclusion, dopamine acts as a hippocampal neurotransmitter that binds to D1- and D2-like receptors and regulates synaptic plasticity involved in depression-related mood.

Summary and future perspectives

In this review, we explored the role of neurotrophic factors and associated signaling pathways, protein kinases, gap-junction proteins, neurotransmitters, and their receptors in the regulation of hippocampal synaptic plasticity in PSD. Alterations in synaptic plasticity in hippocampal neurons are a crucial mechanism for generating depressive symptoms, with LTP and LTD being two important forms of synaptic plasticity. At the molecular level, BDNF and CaMKII in the hippocampus are involved in both LTP and LTD by binding to postsynaptic receptors, exerting a bidirectional modulatory effect on depressive mood. This seemingly contradictory regulation may be due to their release specificity and different postsynaptic sites (Wang et al. 2022). Postsynaptic event-induced alterations in hippocampal synaptic plasticity are key mechanisms underlying the pathology of depression. In addition to regulating postsynaptic activity, the linker protein Cx43 in the hippocampus and monoamine neurotransmitters act as neuromodulators. A growing body of research has shown that monoamine neurotransmitters are released in the synapse, bind to various postsynaptic receptors, and play different roles in depression. These molecules also play a role in regulating hippocampal synaptic plasticity, as neurotransmitters in hippocampal synapses modulate the corresponding postsynaptic receptors. This explains the current clinical use of multiple monoamine antidepressants to treat depression via hippocampal synaptic plasticity mechanisms.

The pathophysiological mechanism of depression involves the dysregulation of synaptic plasticity, leading to synaptic dysfunction, resulting in dendritic atrophy, injury, and reduced spine density. Ultimately, this leads to neuronal cell apoptosis, particularly in brain regions associated with emotions. Our review of multiple factors linked to synaptic plasticity in the hippocampus suggests that altered synaptic plasticity in this region may play a critical role in inducing depressive behavior. Furthermore, studies on hippocampal gene expression indicate that the transcription factor neuronal Per-Arnt-Sim domain protein 4 (NPAS4), which is highly expressed in the hippocampus, inhibits postsynaptic stress-induced neuronal damage. NPAS4 mRNA expression is significantly decreased in rats with PSD (Zhang et al. 2014). The hippocampal microRNA (miRNA) genes miRNA-206-3p, miRNA-206-5p (Guan et al. 2021), and miRNA-124 (Shi et al. 2022) are also implicated in the development of depression. They achieve this by regulating the synthesis of the neurotrophic factor BDNF in the hippocampus. Furthermore, miRNA-26a-3p activates the PTEN–PI3K–Akt signaling pathway to curb neuronal injury and depression-like behavior (Li et al. 2021). Conversely, overexpression of miRNA-140-5p in the hippocampus of ischemic mice inhibited neurogenesis. Clinical trials have also shown that upregulation of this gene could be a possible risk factor for the development of PSD (Liang et al. 2019). These findings underscore the critical role of hippocampal neuronal plasticity in the treatment of depression.
As there is a consensus on the vital role of hippocampal synaptic plasticity in treating mood-related disorders, future studies on PSD should include corresponding functional measurements of hippocampal neurons. Our review revealed that multiple factors in the hippocampus are involved in the pathological process of depression, highlighting therapeutic mechanisms for depressive disorders involving hippocampal synaptic plasticity. These findings can aid in the development of more effective antidepressant drugs.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

N. S. wrote the manuscript. N. S. and WQ. C. reviewed the literature. XM. M. and GM.Z. modified the language. JZ. L. and HY. W. made contributions to the drawing of the figures and tables and the revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Figure legends

Figure 1. LTP and LTD as two forms of hippocampal synaptic plasticity in PSD disease.
Figure 2. Schematic diagram of the pathways involved in BDNF regulation of hippocampal synaptic plasticity. Pro-BDNF binds to sortilin with relatively high affinity and promotes LTD. Pro-BDNF is converted to mature BDNF and binds to hippocampal postsynaptic TrkB to induce its autophosphorylation. The BDNF–TrkB complex enters the cell body and activates different signaling pathways to induce postsynaptic responses. These include the activation of PLCγ1-, PI3K-, and Ras-related pathways, which together activate intracellular CREB phosphorylation, induce its gene transcription in the nucleus, and promote neuronal survival. In addition, the postsynaptic BDNF–TrkB complex induces NMDAR phosphorylation, promotes Ca2+ influx, and activates CaMKII to induce postsynaptic AMPAR phosphorylation. This promotes an increase in postsynaptic glutamate release and postsynaptic currents, facilitating LTP as a form of hippocampal synaptic plasticity.

Figure 3. CaMKII phosphorylation mediates two forms of glutamate receptor regulation involved in synaptic plasticity. a. At the postsynaptic membrane, Ca2+ influx activates CaMKII Thr286 phosphorylation, which not only promotes AMPAR Ser831 phosphorylation, but also promotes AMPAR binding to the phosphorylated protein stargazin, induces stargazin binding to PSD-95, increasing the number of AMPARs at the postsynapse, enhancing glutamate transmission, and promoting hippocampal LTP. In addition, CaMKII phosphorylation can also promote GluN2B binding to the corresponding protein and maintain LTP. b. Presynaptic inhibitory GABA receptors control Ca2+ influx. When NMDAR-mediated Ca2+ influx is attenuated, CaMKII Thr286 phosphorylation activates AMPAR at Ser567, which is involved in inhibiting synaptic enhancement and blocking Ser831 activation. CaMKII phosphorylation also promotes GABA receptor activation, which is involved in LTD.

Figure 4. Hippocampal Cx43 gap-junction channels regulate synaptic plasticity. Ca2+ waves in hippocampal astrocytes activate glutamate and ATP release into the synaptic gap through Cx43 gap-linked channels to promote neurogenesis. Glutamate release activates postsynaptic AMPARs and NMDARs to induce K+ efflux, and Cx43 gap-junction channels couple to take up extracellular K+ and glutamate and redistribute them to enhance LTP, while Cx43 gap linker protein reduces astrocyte volume, increases glutamate and K+ spillover, and inhibits LTP. Another form of Cx43 hemichannels can release neurotransmitters and ATP involved in glutamatergic excitatory synaptic transmission, thereby inducing LTP.

Figure 5. Neurotransmitter-associated receptors regulate hippocampal synaptic plasticity. In the left panel, 5-HT activation of 5-HT7R and 5-HT2CR induces the onset of LTD, and the decrease in BDNF–TrkB signaling induces an increase in 5-HT2AR receptor activity which in turn induces LTD. Regarding DA neurotransmission, the D2-like receptor subtype D4R leads to a decrease in Ca2+ influx through AMPARs, resulting in a decrease in CaMKII activity involved in the onset of LTD. In the right panel, both 5-HT- and DA-related receptors enhance excitatory transmission at hippocampal synapses via CREB-related pathways.