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Review

Eph receptors at synapses: Implications in neurodegenerative diseases

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ABSTRACT

Precise regulation of synapse formation, maintenance and plasticity is crucial for normal cognitive function, and synaptic failure has been suggested as one of the hallmarks of neurodegenerative diseases. In this review, we describe the recent progress in our understanding of how the receptor tyrosine kinase Ephs and their ligands ephrins regulate dendritic spine morphogenesis, synapse formation and maturation, as well as synaptic plasticity. In particular, we discuss the emerging evidence implicating that deregulation of Eph/ephrin signaling contributes to the aberrant synaptic functions associated with cognitive impairment in Alzheimer's disease. Understanding how Eph/ephrin regulates synaptic function may therefore provide new insights into the development of therapeutic agents against neurodegenerative diseases.

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Contents

1. Introduction

Proper cognitive functions depend on the precise assembly of neurons communicating with each other via synaptic transmission. A typical synapse in the central nervous system is comprised of pre- and post-synaptic compartments, together with the surrounding glial cells. Precise regulation of synapse development and plasticity is of particular importance for the proper assembly and integrity of the intricate neuronal network. Aberrant synaptic activity impairs cognitive functions, which is believed to be a major pathological hallmark for various neurological disorders, such as neurodegenerative and psychiatric disorders [1,2]. The molecular mechanisms underlying synapse development and plasticity have been extensively investigated in the past decades. In this review, we focus on Eph receptors, a family of receptor tyrosine kinases (RTKs) that modulate the function of glutamatergic excitatory synapses in the hippocampus, and have been implicated in neurodegenerative diseases such as Alzheimer's disease.

First identified in 1980s, Eph receptors now comprise the largest family of receptor tyrosine kinases (RTKs), which transduce extracellular stimuli into the cells and trigger a variety of signaling cascades

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to regulate neural development [3,4]. Eph receptors are named after an erythropoietin-producing human hepatocellular carcinoma cell line from which the first member was cloned, and their ligands are called ephrins (Eph receptor-interacting proteins). Based on ligand-binding affinity, Eph receptors are classified into two sub-families: EphA family (EphA1-A10) that preferentially binds to ephrinA ligands, and EphB family (EphB1-B6) that possesses high affinity binding domain to ephrinB ligands. A common structure of Eph receptor contains an extracellular ligand-binding domain, a transmembrane domain and an intracellular domain with multiple docking sites for downstream signaling molecules. Like other RTKs, Eph receptors are activated upon ligand binding and their intracellular domains in turn elicit forward signaling in the receptor-expressing cells. In contrast to most of the RTK ligands, however, ephrins are attached to cell membrane, either through a glycosylphosphatidylinositol (GPI) link (ephrinA1-A6) or a transmembrane domain with a short intracellular fragment (ephrinB1-B3). This membrane-anchoring nature of ephrin enables signal transduction in a reverse direction (reverse signaling) during which the extracellular domain of Eph receptor binds to ephrin and activates signaling cascades in the ligand-expressing cells. Thus the Eph/ephrin signaling is more versatile due to its capability of bidirectional signal transduction [3]. The roles of Eph receptors and ephrin ligands are well-established in retinotectal topographic mapping and axon guidance, where the ligands and receptors are expressed in complementary gradients and act primarily as repulsive cues that guide the neurons to their correct targets [5,6]. In recent years, accumulating evidence suggests that Eph receptors are critical regulator in synapse development and plasticity, and their roles in the pathogenesis of neurodegenerative diseases are beginning to be unraveled [7].

2. Eph/ephrin signaling regulates synapse development and plasticity

Formation of synapses begins in early developmental stage with sequential recruitment of a plethora of proteins. Highly motile filopodia on dendrites probe the environment for appropriate presynaptic targets. Reduction of filopodial length is followed by the formation of mushroom-shaped mature dendritic spines, the major sites where the postsynaptic compartments of excitatory synapses reside. A number of Eph receptors and their ligands are localized at the excitatory synapses in the hippocampus, including EphA4, EphB1, EphB2, EphB3, ephrinB2 and ephrinB3 [8–13]. Upon ligand stimulation, tyrosine phosphorylation at the juxtamembrane region of Eph receptors is detected at synapses and colocalizes with postsynaptic marker PSD-95, suggesting that the activation of Eph receptors does occur at synapses [9]. Studies with transgenic mice lacking specific Eph receptors reveal the essential roles of Eph-mediated signaling events at different stages of synapse development, from synapse formation to maintenance and regulation of plasticity.

2.1. Forward signaling

Both EphA and EphB receptors are required for the development of dendritic spines and synapses. Treating cultured hippocampal neurons with ephrinBs at a stage as early as 7 DIV (days *in vitro*) is able to trigger shortening of dendritic filopodia and formation of dendritic spines [14]. Deletion of the genes encoding EphB1, EphB2 and EphB3 completely abolishes the formation of mature dendritic spines, while the spine morphology in single mutant mice is grossly normal, indicating their critical and redundant roles in promoting spine formation [8]. The triple EphB mutant neurons develop synapses on the dendritic shafts rather than at the dendritic spines, indicating the blockade of synapse maturation or alteration of synaptic efficacy [15]. More importantly, clusters of two subtypes of glutamate receptors, NMDA receptors and AMPA receptors are greatly reduced in the filopodia and dendrites of the triple mutant mice, suggesting that synaptic functions are impaired in these mutant mice [8]. Contrary to what has been observed for EphB receptors, activation of EphA4 by ephrinA triggers the reduction of dendritic spines and synaptic proteins (e.g. PSD-95 and GluA1), emphasizing the essential role of EphA4 in the retraction of dendritic spines and elimination of excitatory synapses [9,10,16].

The role of Eph receptors in spine and synapse development changes during neuronal development. In cultured hippocampal neurons, perturbing the function of EphB receptors leads to a marked drop in synapse number during the second week, while no obvious effect could be observed before 7 DIV (days *in vitro*) or after 14 DIV. The role of EphB receptors in spine stabilization is evident for cultured neurons at 21 DIV [17]. On the other hand, activation of EphA4 destabilizes spines and synapses in mature neurons, while its significance on synapse formation at early stage is unclear [9,16,18]. However, another member of EphA family, EphA5, induces dendritic spine formation and synaptogenesis in early developmental stages, indicating the distinct roles of EphA receptors during synapse development [19].

How does Eph/ephrin forward signaling direct synapse development? Accumulating evidence suggests that Eph receptors coordinate multiple key signaling molecules at the synapses, including actin cytoskeleton regulators, neurotransmitter receptors and the ubiquitin–proteasome system. It is believed that Eph receptors regulate the activity of Rho-GTPases through their upstream regulators, GEFs (guanine-nucleotide exchanging factor) and GAPs (GTPase-activating proteins), which facilitate the reorganization of actin cytoskeleton and lead to morphogenesis of dendritic spines [9, 20–24]. Specifically, EphB receptors stabilize the actin cytoskeleton network through activation of GEF kalirin, intersectin or Tiam1-mediated activation of the Rho GTPases Rac1 and Cdc42, while EphA4 promotes spine shrinkage through increased activity of RhoA and its corresponding GEF ephexin1. In addition, Eph receptors also directly control the actin-binding proteins at synapses. ADF (actin depolymerizing factor)/cofilin is a key family of actin destabilizing factors. EphA4 induces actin depolymerization activity of cofilin through PLC-γ, while EphB2 inhibits cofilin by FAK (focal adhesion kinase)-mediated phosphorylation, thereby dynamically regulating dendritic spine morphology [25,26].

In addition to regulating the cytoskeleton dynamics during synapse development, Eph receptors also directly regulate the function of postsynaptic neurotransmitter receptors. EphB2 interacts with GluN1 subunit of NMDA receptor through its extracellular domain. Activation of EphB receptors by ephrinBs induces the co-clustering of NMDA receptor and specific postsynaptic proteins including calcium/calmodulin-dependent protein kinase II (CaMKII) and Grb10 [27]. More importantly, EphB2 phosphorylates NMDA receptors and enhances Ca^{2+} influx, leading to Ca^{2+}/cAMP-responsive element binding protein (CREB)-dependent transcription of immediate early genes (e.g. *bdnf* and *c-fos*) that may contribute to synapse development [27,28]. EphB2 is also suggested to associate with AMPA receptors through interaction with glutamate receptor-interacting protein 1 (GRIP1) that depends on the PDZ binding motif on the C-terminal of EphB. Interfering with this interaction abolishes the colocalization of EphB2 and AMPA receptors [29]. Since EphB phosphorylates synaptojanin 1, a phosphatidylinositol 5′-phosphatase that is involved in clathrin-mediated endocytosis, EphB activation might regulate the internalization of AMPA receptors [30]. It is recently found that the role of EphB2 in potentiating NMDA receptor activity and maintaining AMPA receptor synaptic expression is negatively regulated by the *cis*-interaction with its ligand ephrinB3 on postsynaptic membrane, providing an inhibitory pathway to fine-tune EphB2-mediated synaptogenesis [31].

Interestingly, recent findings reveal novel mechanisms underlying the roles of Eph receptors at synapses that involve proteosome-dependent protein degradation. Different from its conventional role in GEF activation, EphB2 triggers degradation of the RhoA-GEF ephexin5 through the ubiquitin-proteasome system. Ephexin5 is a negative regulator of synapse development, thus its degradation by EphB activation accelerates synapse formation [32]. This mechanism is

believed to control the appropriate timing of synapse formation. Similarly, EphA4-dependent degradation of AMPA receptor subunit GluA1 also serves as a safeguard system to prevent synapses from overstimulation during homeostatic plasticity. EphA4 activates the ubiquitin-mediated protein degradation pathway through interaction with the ubiquitin ligase anaphase-promoting complex (APC), removing GluA1 from synapses and reducing synaptic strength during prolonged elevation of synaptic activity [16].

2.2. Reverse signaling

Besides the forward signaling described above, reverse signaling mediated by ephrin ligands also plays pivotal roles in synapse development. For example, ephrinB activation at the post-synaptic sites reduces the length of filopodia and promotes spine formation, which can be blocked by a C-terminally truncated form of ephrin-B1, indicating the requirement of ephrinB intracellular domain in transducing synaptic signals. Upon activation, ephrinB recruits GIT1 (G protein–coupled receptor kinase–interacting protein) through its synaptic binding partner Grb4 (growth factor receptor-binding protein 4), thus promoting the formation of dendritic spines and synapses [33]. It was recently reported that by binding to presynaptic EphB2, ephrinB3 upregulates synapse number by inhibiting MAPK (mitogen-activated protein kinase) pathway at the postsynaptic neurons [34]. Similar to what has been observed in EphB triple knockout mice, deletion of ephrinB3 gene shifts the synapses from dendritic spines to dendritic shafts, suggesting that the synaptic deficits in EphB triple knockout mice is, at least in part, due to abnormal reverse signaling [8,34].

The role of reverse signaling is not restricted to the postsynaptic sites. Previous knockdown study found that loss of postsynaptic EphB2 eliminates the clusters of presynaptic vesicle protein SV2, raising the possibility of ephrinB reverse signaling in presynaptic differentiation [29]. Indeed, ephrinB1 and ephrinB2 are both expressed at presynaptic terminals, which act synergistically to recruit the active zone organizing protein syntenin-1 to potentiate presynaptic specialization in cortical neurons [35]. Although ephrinAs do not possess a C-terminal fragment for intracellular signaling, they are able to associate with other cell surface receptors, such as neurotrophin receptor TrkB to trigger presynaptic differentiation in retinal axons [36]. However, the importance of ephrinA-mediated presynaptic specialization in the hippocampus remains to be determined.

2.3. Eph/ephrin-mediated signaling is essential for synaptic plasticity

Studies through targeted deletion of Eph receptor genes or overexpression of mutant Eph receptors have significantly advanced our understanding of their roles in synaptic plasticity. Loss of EphB2 abolishes long-term potentiation (LTP) in hippocampal perforant path. However, in Schaffer collateral CA3–CA1 pathway, depletion of EphB2 does not have obvious impact on the early phase LTP (E-LTP), while it is required for the later phase LTP (L-LTP) and long-term depression (LTD). Interestingly, deficits in L-LTP could be completely rescued by overexpression of EphB2 extracellular domain fused with β-galactosidase, indicating that the intracellular domain and kinase activity of EphB2 are not required for regulating certain forms of synaptic plasticity at CA1 synapses [37,38]. It was proposed that the *cis*-interaction of postsynaptic EphB2 with NMDA receptors through their extracellular domains or *trans*-interaction of axonal EphB2 with postsynaptic ephrinBs are critical at CA3–CA1 synapses [4]. While the reverse signaling mediated by postsynaptic ephrinBs is required for hippocampal LTP [7,11,39,40], the exact mechanisms require further investigation. Similar to EphB2, the deletion of EphA4 also blocks CA3–CA1 LTP and LTD in a kinase-independent manner. While EphA4 does not directly interact with NMDA receptor and loss of presynaptic EphA4 in CA3 neurons does not affect CA3–CA1 LTP, it is currently believed that the role of EphA4 on LTP requires the reverse signaling mediated by its glia-derived ligand ephrinA3, and involves regulation of the expression of glial glutamate transporter [11,41].

Besides regulating the Hebbian form of synaptic plasticity, Eph receptors have also been found to regulate homeostatic plasticity, which balances the activity of neuronal network. Our laboratory has previously reported that sustained synaptic activity activates EphA4, which in turn reduces the amplitude of miniature excitatory synaptic current (mEPSC), thus fine-tuning the strength of the excitatory synapses [16]. These findings collectively underscore the key roles of Eph receptors in synaptic plasticity.

3. Deregulation of Eph/ephrin signaling leads to synaptic deficits associated with Alzheimer's disease

Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, are devastating neurological disorders characterized by the gradual loss of neuronal structures and cognitive functions. A number of cellular mechanisms have been associated with the pathogenesis of neurodegenerative diseases, such as genetic mutations, and deregulation of protein processing, trafficking and degradation. However, the precise molecular programs that lead to these diseases remain elusive.

3.1. Synaptic failure is an early pathological marker of Alzheimer's disease

Progressive loss of cognitive functions in Alzheimer's disease is associated with the impairment of synaptic connections and death of neurons. Decline in cognitive ability exhibits a correlation with the drop of synapse number in Alzheimer's disease patient and loss of synaptic proteins occurs at a very early stage of disease onset [42,43]. Impairment of synaptic transmission and plasticity have been observed in various mouse models of Alzheimer's disease [44]. The senile plaques resulting from abnormal aggregation of β-amyloid (Aβ) and the neurofibrillary tangles composed of hyperphosphorylated tau protein are the most characteristic pathological features associated with Alzheimer's disease [45]. Aβ peptides are generated from amyloid precursor protein (APP) by a series of enzymatic cleavage, among which $Aβ_{1–42}$ is the most toxic form to neurons. Mutations in APP and presenilin 1, the core component in γ-secretase complex that is critical for Aβ generation, are closely associated with familial Alzheimer's disease. It is proposed that an appropriate physiological level of Aβ is important for presynaptic function, while production of pathological Aβ impairs postsynaptic structures, leading to loss of dendritic spines and synapses [44]. Interestingly, accumulation of Aβ facilitates the aggregation of Tau, which in turn plays an indispensable role in Aβ-induced synaptic deficits [46–49]. Tau is a microtubule-binding protein that stabilizes the axonal cytoskeleton for effective axon transport. Hyperphosphorylation of tau in pathological condition dissociates it from microtubule and results in neurotoxic aggregations. Several kinases that phosphorylate Tau have been linked to Alzheimer's disease, such as glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5 (Cdk5) [50,51]. Disease-associated Tau mutants accumulate at dendritic spines much earlier than the loss of synapses, where they impair the synaptic targeting of AMPA receptors and NMDA receptors [52]. Failure of synaptic function is believed to be one of the early and major pathological events in Alzheimer's disease. Thus, elucidating the signaling pathways associated with synaptic deficits will provide significant insights into the underlying pathophysiological mechanisms and the development of therapeutics.

3.2. Expression of Eph receptors is associated with Alzheimer's disease

Synaptic failure in Alzheimer's disease is accompanied by changes of synaptic protein composition and function. A dramatic reduction of EphA4 and EphB2 receptor in the hippocampal tissues has been

recently observed in stage II-III Alzheimer's disease patients with only very mild cognitive deficits [53]. This is the first demonstration that the expression level of Eph receptors is associated with Alzheimer's disease. Interestingly, in the mouse model of Alzheimer's disease in which mutant human APP is overexpressed, changes in EphA4 and EphB2 expression and their downstream signaling in the hippocampus can be detected at 2-months, which is much earlier than the reduction of synaptic proteins and the onset of cognitive decline, suggesting that Eph receptors may be a critical factor that leads to synaptic failure and cognitive impairment in Alzheimer's disease. The next question is how Eph receptors are involved in the deterioration of synaptic functions, such as structural stability of synapse, neurotransmitter release and synaptic transmission during the pathogenesis of Alzheimer's disease.

3.3. Eph receptors are involved in the destabilization of synaptic structures associated with Alzheimer's disease

Some early reports show that Eph/ephrin signaling upregulates Tau expression and phosphorylation, while the significance of this regulation in pathological conditions is unclear [54,55]. On the contrary, accumulating evidence suggests a crosstalk between Eph receptor and the pathways mediating Aβ generation and toxicity. Aberrant activity of γ-secretase, the key enzyme that cleaves APP to generate Aβ leads to cognitive impairment as demonstrated in various transgenic mouse models for Alzheimer's disease [56,57]. As a γ-secretase substrate, EphA4 colocalizes with γ-secretase at the synaptic lipid raft fraction and is processed by γ-secretase upon synaptic activity to generate a short intracellular domain (EphA4-ICD) [58]. Unlike ICDs of other proteins which translocate into the nucleus to regulate gene expression, EphA4-ICD activates Rac1 and induces the formation of dendritic spines [58–60]. Interestingly, Alzheimer's disease-related familial mutations of presenilin 1(PS1) hinders the cleavage of EphA4, suggesting that reduced formation of dendritic spines resulted from the attenuated processing of EphA4 may be a major cause of synaptic failure in Alzheimer's disease [58]. This idea is further supported by the observation of reduced PAK1 activity and pathological cofilin aggregates in Alzheimer's disease patients and mouse models, since the actions of PAK1 and cofilin are tightly controlled by Rac1, the major effector of EphA4-ICD during spine formation [61].

Similar to EphA4, the processing of EphB2 receptor is also mediated by γ-secretase, which can be inhibited by certain PS1 familial Alzheimer's disease mutations [62,63]. Considering the importance of C-terminal fragment of EphB2 in the maintenance of NMDA receptor surface expression, reduced processing of EphB2 may lead to deficits in NMDA receptor-dependent synaptic transmission and plasticity under pathological conditions [63]. However, the processing of EphB2 is apparently not affected in the mouse model of Alzheimer's disease overexpressing mutant human APP [64]. Instead, the Aβ peptide exhibits a high affinity to the extracellular domain of EphB2 and directs EphB2 to the proteasome-mediated protein degradation machinery, resulting in the marked reduction of surface and total EphB2 in neurons, which may account for the loss of dendritic spines and synaptic proteins [64,65]. More importantly, the impairment of synaptic plasticity and cognitive function caused by Aβ accumulation can be rescued by restoring EphB2 level [64]. These results suggest that the aberrant processing and clearance of EphB2 caused by γ-secretase dysfunction and Aβ accumulation, respectively, are two critical pathological events in Alzheimer's disease.

3.4. Eph/ephrin-regulated synaptic transmission is implicated in Alzheimer's disease pathology

As the major neurotransmitter in the brain, glutamate activates different subtypes of receptors at neuronal synapses, such as NMDA receptors, AMPA receptors and metabotropic glutamate receptors (mGluRs). A well-controlled pool of glutamate at synapses is crucial, as insufficient glutamate attenuates the efficacy of synaptic transmission, while excessive glutamate can result in several types of synaptic dysfunction, including excitotoxicity that causes cell death, desensitization of glutamate receptors that lead to synaptic depression, and activation of perisynaptic receptors that facilitates long-term depression [66,67]. The steady level of synaptic glutamate is maintained by GLAST (glia-specific glutamate/aspartate transporter) and GLT-1 (glutamate transporter-1), two abundant glutamate transporters at the perisynaptic astrocytes through controlling the uptake of glutamate from the synaptic cleft [68]. The protein levels of the two glutamate transporters are tightly controlled by Eph receptor-mediated reverse signaling [41,69]. Genetic deletion of glial ephrinA3 or its postsynaptic binding partner EphA4 dramatically increases the expression of GLAST and GLT-1 and impairs learning and memory performance in the transgenic animals. On the other hand, overexpression of ephrinA3 in astrocytes increases synaptic glutamate concentration by downregulating the glutamate transporters, leading to degeneration of dendrites and increased susceptibility to epileptic seizures, two phenotypes that are closely associated with Alzheimer's disease [44,70]. Interestingly, Aβ itself exhibits an inhibitory effect on glutamate uptake and leads to synaptic depression [71,72]. Therefore, it would be interesting to further investigate whether and how Aβ regulates glutamate level at the synaptic cleft through Eph receptors and their ephrin ligands.

Metabotropic glutamate receptors (mGluRs) are cell surface G-protein coupled receptors (GPCRs) that modulate synaptic functions through second messenger pathways. Group I mGluRs, including mGluR1 and mGluR5, are predominantly expressed at the postsynaptic membranes. Pharmacological inhibition of mGluRs blocks Aβ-induced synaptic depression, indicating their vital roles in Alzheimer's disease pathology [73]. Interestingly, mGluR1 forms a functional complex with ephrinB2 and GluN1 subunit of NMDA receptor. Activation of mGluR enhances NMDA-induced excitotoxicity to neurons, which is augmented upon the presence of active ephrinBs [74]. In addition, mGluR-dependent LTD can be further enhanced by activation of synaptic ephrins, suggesting that the action of mGluR at synapses is under the control of Eph/ephrin signaling and ephrinBs may act synergistically with mGluR to facilitate Aβ-induced excitotoxicity and synaptic depression [75]. Attenuating mGluR function by interfering Eph/ephrin signaling may be beneficial during Aβ-induced synaptic deterioration.

The on and off status of glutamate receptors is not simply controlled by glutamate. D-serine, an isomer derived from L-serine by serine racemase, binds to the glycine site of NMDA receptors and potentiates NMDA receptor-dependent synaptic current [76,77]. Blockade of astrocytic release of D-serine abolishes LTP induction in the hippocampus [78]. Moreover, reduced serine racemase and D-serine levels has been observed in aging hippocampus or in the serum of Alzheimer's disease patients, consistent with the idea that lack of D-serine leads to NMDA receptor hypofunction implicated in cognitive deficits [79–81]. A recent study shows that ephrinB3 expressed in postsynaptic neurons is able to trigger the astrocytic production of D-serine in a manner dependent on astrocytic EphB3 and EphA4 receptors, augmenting the interaction between PICK1 (protein interacting with C-kinase) and serine racemase through PKCα (protein kinase C α) inactivation [82]. Although the reduced expression of Eph receptors is obvious in Alzheimer's disease patients [53], it is especially important to further characterize the precise regulation of Eph receptor expression in astrocytes during disease progression in order to understand the role of Eph-regulated D-serine production in the pathogenesis of Alzheimer's disease. It is noteworthy that acute treatment of Aβ augments serine racemase expression and D-serine release in microglia, suggesting that an elevated D-serine level occurs at least at the early stage of Alzheimer's disease [83]. Thus, it is intriguing to speculate that there might be a similar upregulation of Eph

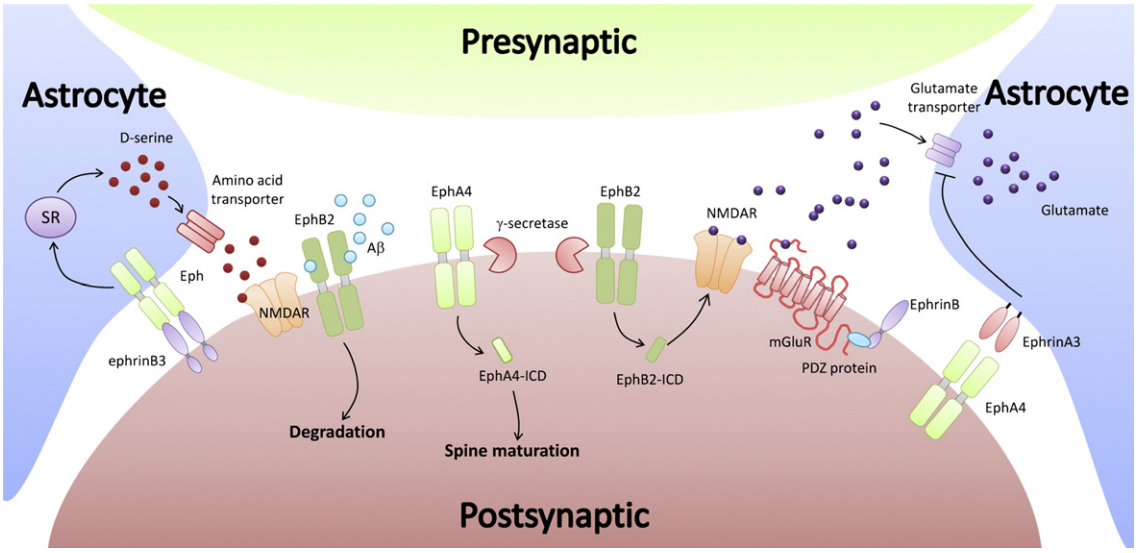

Fig. 1. Signaling pathways mediated by Eph/ephrin are implicated in the synaptic failure associated with Alzheimer's disease. Eph receptors and their ephrin ligands are critical regulators of synaptic functions in the central nervous system. Deregulation of Eph/ephrin signaling results in synaptic deficits that are associated neurodegenerative diseases, e.g. Alzheimer's disease. (1) EphA4 and EphB2 receptors are processed by γ-secretase, generating the ICDs (intracellular domains) to regulate synaptic function. This process could be inhibited by Alzheimer's disease-related familial mutation of presenilin 1 (PS1), the active component of γ-secretase. Furthermore, EphB2 is quickly degraded upon binding to the Aβ peptide, leading to the impairment of synaptic plasticity. (2) EphrinB forms a complex with mGluR, which may probably facilitate Aβ-induced excitotoxicity and synaptic depression through NMDAR. (3) Serine racemase (SR) expression and D-serine release in glia can be enhanced by *trans*-activation of glial EphB3 and EphA4 receptors. (4) Overactivation of glial ephrinA3 by postsynaptic EphA4 inhibits glutamate uptake by glial glutamate transporter GLAST and GLT-1. Similarly, Aβ blocks the glutamate uptake by glial, leading to synaptic depression. The exact mechanism underlying the action of Eph receptors and Aβ during D-serine release and glutamate uptake awaits further investigation.

receptors at the stage preceding the subsequent decline of Eph receptors expression.

4. Perspectives

The development of functional synapses depends on the coordination of a plethora of signaling molecules to ensure the accurate transmission of neuronal signal from presynaptic nerve terminal to postsynaptic compartment. Deregulation of these signaling cascades is associated with transition from physiological condition to the pathological state. Eph receptors and their ephrin ligands are enriched at excitatory synapses and changes in Eph function are thought to be characteristic of early events in Alzheimer's disease (Fig. 1). However, whether the expression profiles of ephrins are regulated during the disease progression is not well understood, especially at the very early stage. It would be very important to identify the key stimulus that triggers the change in their expression profiles and characterizes the underlying mechanisms. Furthermore, EphA and EphB receptors appear to play opposite roles in synapse development, both of which are indispensable for the normal function of synapses. Thus, it is of particular importance to investigate where the crosstalk between EphA and EphB occurs and how the balance between EphA and EphB is perturbed under pathological conditions. Our laboratory has previously shown that EphA directs cyclin-dependent kinase 5 (Cdk5), a critical kinase in the pathogenesis of Alzheimer's disease, to promote spine elimination [9,50]. It would be of interest to further investigate whether and how Cdk5-regulated Eph signaling is involved in Alzheimer's disease. Considering the importance of Eph/ephrin signaling in shaping functional synapses, small molecules that modulate the activity and stability of Eph receptors would be attractive therapeutic candidates for Alzheimer's disease. Indeed, some compounds and peptides have been demonstrated to antagonize the ligand binding ability of Eph receptors [84–86]. Further identification of these small molecules and examination of their therapeutic activity would be beneficial for developing treatment for Alzheimer's disease.

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