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Current Opinion in Neurobiology

Regulation of postsynaptic signaling in structural synaptic plasticity

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Morphological changes of dendritic spines are strongly associated with synaptic development and synaptic plasticity, which underlies learning and memory. These changes are driven by alterations of F-actin dynamics under the control of Rho GTPases or by synaptic trafficking and insertion of glutamate receptors. Understanding the molecular events that occur during the formation and stabilization of dendritic spines, and the signaling pathways regulating these processes, provides insights into the mechanisms of learning and memory. In this review, we discuss the recent advances on these postsynaptic signaling pathways, in particular, we discuss the specific signaling events that couple the cell-surface receptors to intracellular targets. In addition, we discuss the deregulation of these signaling pathways and their subsequent impact on synaptic dysfunction in Alzheimer's disease.

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Current Opinion in Neurobiology 2017, **45**:148–155

This review comes from a themed issue on **Molecular neuroscience**

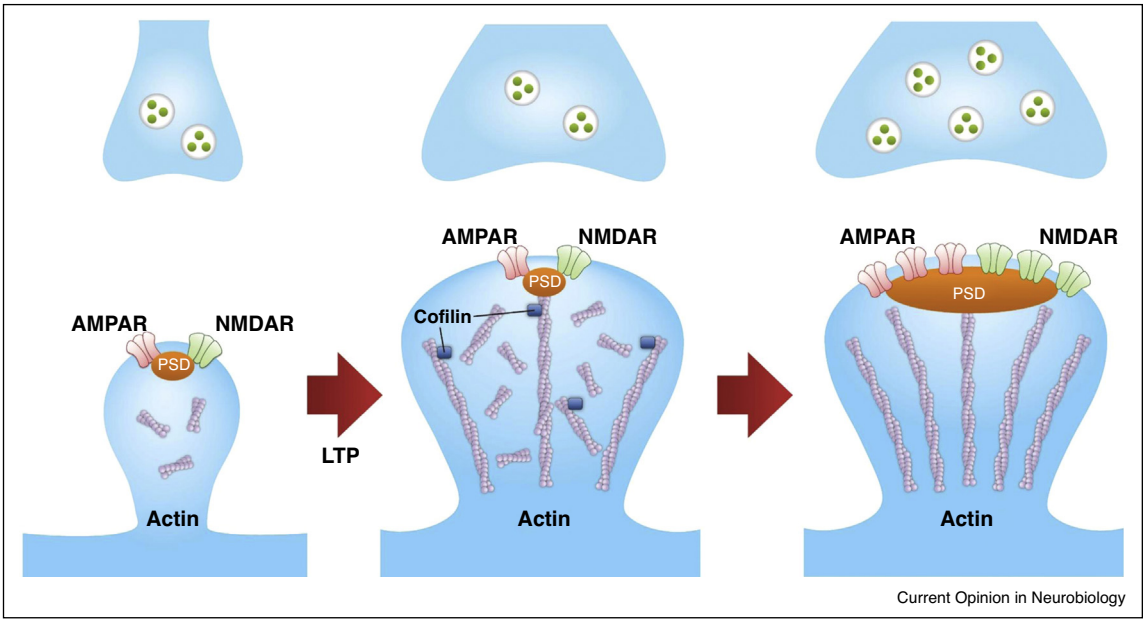
Edited by **Susumu Tomita** and **Brenda Bloodgood**

http://dx.doi.org/10.1016/j.conb.2017.05.016

Dendritic spines, which are the specialized protrusions on dendrites where most excitatory synapses reside, receive and integrate information in the brain [1•]. They are the sites where ionotropic glutamate receptors (including both AMPA-type and NMDA-type glutamate receptors) are concentrated to mediate efficient excitatory synaptic transmission [2]. Dendritic spines are morphologically diverse and can be classified as cup-shaped, mushroom, stubby, thin, or filopodial spines [3]. For example, mushroom spines have large heads and thin necks, whereas stubby spines have large heads and no neck. The heads of dendritic spines comprise a thickened postsynaptic density (PSD), which contains scaffold, cytoskeletal, and motor proteins to support and stabilize glutamate receptors [4]. While dendritic spines are highly motile and dynamic, the structural changes of spines are associated with changes in synaptic efficacy [5]. Indeed, changes of spine number, size, and morphology, which are collectively termed structural synaptic plasticity, are highly correlated with the abundance of PSD and organization and localization of AMPA-type glutamate receptors (including their abundance, subtypes, and properties) at the postsynaptic sites [6]. This results in the regulation of synaptic strength, which is termed functional synaptic plasticity [7]. The molecular regulation of structural and functional plasticity can be independent; for example, overexpression of a nuclear receptor, Nr4a1 (nuclear receptor subfamily 4, group A, member 1), was recently shown to result in dendritic spine loss without affecting the excitatory synapses or synaptic transmission [8]. Nonetheless, in most cases, structural synaptic plasticity is tightly coupled with functional synaptic plasticity.

Experience-regulated structural synaptic plasticity, specifically changes in dendritic spine density and shape, is critical for learning and memory [2]. For instance, enhanced spine formation is associated with the improved performance after learning [9]. Motor learning experience induces the rapid formation of dendritic spines in the mouse motor cortex [9], and the continuation of the training task stabilizes the learning-induced spines [10]. Importantly, repetitive postsynaptic depolarization, which induces long-term potentiation (LTP), promotes spine enlargement [11]. In contrast, weakening of synaptic connections during long-term depression (LTD) results in the shrinkage of dendritic spines [12]. The modulation of synaptic strength involves stepwise changes of different structural elements of synapses, including the volumes of presynaptic boutons and postsynaptic spines, pools of synaptic vesicles, areas of active zones, and composition of the PSD; these changes are closely coordinated to ensure efficient neurotransmission [7]. Two-photon time-lapse imaging, glutamate uncaging, and electron microscopy studies recently revealed the dynamic correlation between spine morphological changes and the composition of subsynaptic structures in CA1 pyramidal cells in cultured hippocampal slices (Figure 1). Synaptic activity stimulates the enlargement of dendritic spines. This is followed by the trafficking of

Figure 1



Structural synaptic plasticity is initiated by the coordinated growth of dendritic spines and increased actin within the dendritic spines. The formation of stabilized structural and functional synapses requires initial spine growth, followed by an increase of postsynaptic density and subsequent presynaptic boutons.

structural PSD proteins (*i.e.*, Homer1c) to dendritic spines along with the subsequent coordinated increase in the size of presynaptic boutons and PSD, which stabilizes the enlarged spines and functional synapses [13]. The concurrent increases in the size of spines, presynaptic boutons, and the PSD are critical for synaptic plasticity, suggesting that dendritic spine morphology plays a crucial role in synaptic plasticity. In this review, we focus on the recent advances in the postsynaptic signaling mechanisms that regulate dendritic spine morphology as well as their deregulation in spine loss and dysfunctions in Alzheimer's disease (AD).

Two major postsynaptic mechanisms that underlie spine enlargement and synapse potentiation are actin remodeling of spines and synaptic insertion of AMPA-type glutamate receptors [2,14]. Dendritic spine morphology is tightly regulated by the dynamics of F-actin, which is the major cytoskeletal component of dendritic spines [15]. During spine enlargement, actin polymerization and the stable pool of F-actin increase rapidly within the stimulated spines, which promote the expansion of spines and anchoring of synaptic proteins in CA1 pyramidal cells of hippocampal slices [11,16]. Indeed, after LTP induction, the composition of actin-binding proteins changes in the spines. Cofilin, a key regulator of actin dynamics, accumulates rapidly in dendritic spines [17•]. Binding of cofilin to F-actin severs actin filaments, which results in the generation of new barbed ends for additional actin growth [18]. Cofilin also exerts distinct effects on actin polymerization in a concentration-dependent manner: at low concentrations, cofilin depolymerizes F-actin by severing actin filaments, whereas at high concentrations, cofilin enhances F-actin nucleation and assembly [19]. The high local concentration of cofilin in stimulated spines suggests that cofilin promotes F-actin nucleation and polymerization [19]. Moreover, the concentration of F-actin in the spines leads to spine expansion and increases the number of docking sites at postsynaptic sites that capture the newly synthesized proteins [20]. Thus, the new F-actin formed at the enlarged spines may serve as a synaptic tag for the consolidation of the potentiated state, which is critical for the maintenance of LTP.

The modification of the F-actin cytoskeleton during dendritic spine plasticity is also regulated by actin regulators, in particular, the small Rho GTPases including Rac1, Cdc42, and RhoA [21,22]. During LTP induction, activation of NMDA-type glutamate receptors mediates calcium influx into the spines; this is followed by the transient activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which results in the activation of Rho GTPase and actin polymerization during spine plasticity [23]. While Rho GTPases serve as major links that couple extracellular signals to actin dynamics in spines [24], proteins switching between their active GTP-bound

and inactive GDP-bound states promotes or suppresses the polymerization of actin filaments, respectively. Rho GTPase activation is stimulated by guanine nucleotide exchange factors (GEFs), whose inactivation is mediated by GTPase-activating proteins (GAPs) [25••]. Rac1 and Cdc42 activation are well known to stimulate F-actin polymerization, which promotes spine formation and enlargement. RhoA activation results in spine shrinkage through its effector RhoA kinase and actomyosin reorganization [26]. NMDA receptor activation induces the phosphorylation and activation of the Rac GEFs such as Tiam1 and Kalirin-7 in cultured neurons. The resultant activation of Rac1 mediates spine enlargement [27,28] through the activation of downstream effectors – the serine/threonine kinase p21-activated kinase (PAK) and LIM-kinase-1 (LIMK-1) – which ultimately inhibits the activity of cofilin [29]. However, it remains unclear how different Rho GTPases act and how they are coordinated in activity-dependent spine morphogenesis and the maintenance of structural plasticity. The recent findings on the precise spatiotemporal regulation and dynamic control of Rho GTPases regulated by specific cell-surface receptors within spines [30••,31] may provide some hints about how the compartmentalized Rho GTPases couple the extracellular cues to spine morphology.

BDNF–TrkB signaling

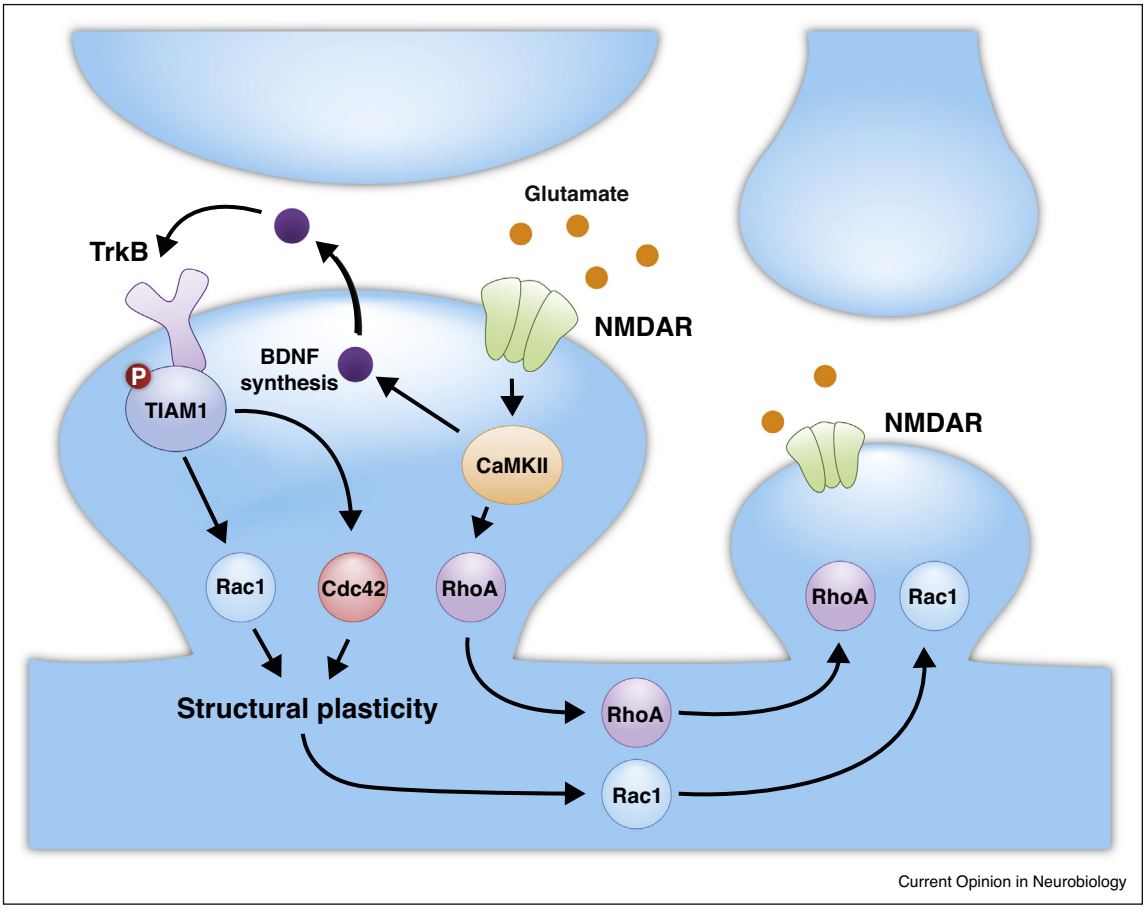
The receptor tyrosine kinase, TrkB, which is activated by its neurotrophin ligand brain-derived neurotrophic factor (BDNF), is well known to play crucial roles in activity-dependent structural plasticity in the hippocampus. During LTP, BDNF–TrkB signaling shapes structural plasticity by mediating actin cytoskeletal changes and synaptic protein reorganization [6,32]. The BDNF-stimulated tyrosine phosphorylation and activation of TrkB lead to F-actin stabilization and dendritic spine enlargement by increasing the activity of PAK and inducing the inhibitory phosphorylation of cofilin, which contribute to the consolidation of LTP [33]. TrkB is also suggested to regulate F-actin remodeling through the Rac/RhoA GEF, Vav, to activate Rac, which is required for the modulation of activity-dependent synaptic plasticity in cultured mouse hippocampal slices [34]. In addition to the tyrosine autophosphorylation of TrkB, the serine phosphorylation of TrkB by the serine/threonine kinase, cyclin-dependent kinase 5, (Cdk5) is required for activity-induced spine remodeling, as demonstrated in the hippocampal slices derived from TrkB phosphorylation-deficient knockin mouse [35]. The action is mediated through the enhancement of the interaction between the receptor and Tiam1, leading to Rac1 activation and the modulation of cofilin activity. Accordingly, recent sophisticated glutamate uncaging and imaging studies have revealed the complex interplay of BDNF–TrkB signaling in the activity-dependent synaptic plasticity in rat and mouse hippocampal slices at the single-spine scale. Synaptic activity enhances the local synthesis and release of BDNF from postsynaptic dendrites; autocrine BDNF–TrkB signaling not only triggers the enlargement of the stimulated spines, but also enhances the crosstalk between the stimulated spines and their neighboring spines to coordinate structural plasticity among the stimulated and unstimulated neighboring spines [36••] (Figure 2). The activated BDNF–TrkB signaling within the stimulated dendritic spines mediates the concurrent activation of Cdc42 and Rac1 in a distinct spatiotemporal pattern [30••], whereas synaptic activity rapidly stimulates RhoA independent of the postsynaptic BDNF–TrkB signaling. While Cdc42 activity is restricted to the stimulated spines to promote the synapse-specific plasticity, activated Rac1 together with RhoA signals propagate from the stimulated spines to the neighboring unstimulated spines to facilitate the structural plasticity of the neighboring spines. Hence, elucidating the specific roles of these BDNF–TrkB-dependent and BDNF–TrkB-independent Rho GTPase signals and their spatiotemporal coordination will provide insights into the mechanisms that underlie structural and functional synaptic plasticity.

Ephrin–Eph signaling

The Eph (erythropoietin-producing hepatocellular) family, which comprises EphA and EphB members, is another family of receptor tyrosine kinases that have well-established roles in the regulation of dendritic spine morphology and postsynaptic organization [37]. The interaction of Ephs with their cell-surface ligands, ephrins, results in bidirectional signaling. Mice in which EphBs are deleted exhibit decreased spine and synapse density in the hippocampus [38]. Activation of EphB forward signaling promotes spine morphogenesis and maturation through the coordinated activation of Rac1 and Cdc42. Independent studies demonstrate that EphB2 activation enhances the recruitment and phosphorylation of the Rac GEFs, Tiam1 and Kalirin-7, resulting in the activation of Rac1 and subsequent spine formation in cultured neurons [39,40]. EphB2 also activates Cdc42 through its interaction with the Cdc42 GEF, intersectin-1 [39]. The positive action of EphB on spine morphogenesis can also be regulated by a negative signaling pathway. The spine-promoting activity of EphB is suppressed by its binding with a RhoA GEF, ephexin5 [41]. The ephrinB-dependent activation of EphB causes the phosphorylation-dependent ubiquitin proteasomal degradation of ephexin5, which subsequently relieves the inhibition and consequently initiates spine promotion.

The induction of LTP facilitates synaptic potentiation, which may lead to runaway excitation. To maintain the stability of neuronal network activity, neurons adopt a compensatory mechanism, termed homeostatic synaptic plasticity, in order to prevent runaway excitation [42]. In particular, prolonged elevation of neuronal activity decreases synaptic strength, which prevents hyperexcitation. Indeed, chronic neuronal activity decreases synaptic

Figure 2

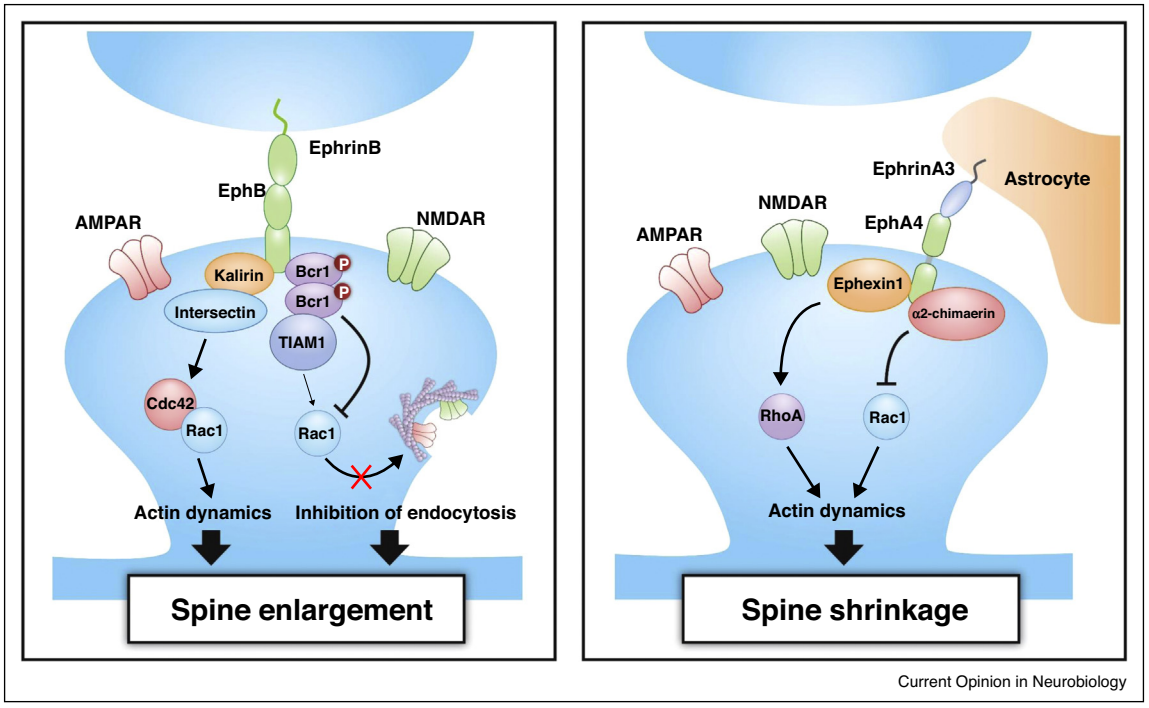


Local BDNF–TrkB–Rho GTPase signaling is required for synaptic crosstalk. Synaptic activity stimulates the local synthesis and release of brain-derived neurotrophic factor (BDNF), which induces the activation of its receptor, TrkB, at the same spines and results in the activation of the Rho GTPases, Cdc42 and Rac1. Only activated Rac1, together with activated RhoA stimulated by NMDA receptor, will be transported to the neighboring dendritic spines. The spread of active Rac1 and RhoA into the neighboring spines primes the spines to undergo structural plasticity even when a weak stimulus is received.

strength through the activation of the Eph family member, EphA4, in cultured hippocampal neurons [43]. In the hippocampus, stimulation of postsynaptic EphA4 in the CA1 pyramidal neurons by its ligand, ephrinA3, which is expressed in astrocytes also causes dendritic spine retraction through the activation of RhoA activity and reduces the number of excitatory synapses [44]. EphA4 activation enhances the recruitment of Cdk5 to the receptor and increases Cdk5 activity; in turn, Cdk5 phosphorylates the RhoA GEF ephexin1 and modulates the actin cytoskeleton in hippocampal neurons via increased RhoA activity [45].

The major outstanding research question about Eph and spine morphogenesis is how EphBs or EphAs co-regulate the activities of different GEFs and GAPs and act in concert to precisely regulate Rho GTPase signaling in synaptic plasticity. The following examples may provide some hints (Figure 3). At synapses, EphB interacts with the Tiam1 (a Rac GEF) and Bcr (a Rac GAP), which have opposing effects on Rac1 activity [31]. Neurons lacking Bcr have more and larger spines than the control neurons Nonetheless, Bcr deletion switches EphB-mediated spine formation to spine retraction. Given that Bcr1 restricts Rac1 activity and limits the Rac-mediated EphB internalization induced by ephrinB, the coordinated activation of Tiam1 and Bcr upon EphB activation enables the precise regulation of Rac1 activity and spine morphology. On the other hand, EphA4 activation stimulates the Rho GEF ephexin1 and the Rac GAP α2-chimaerin to activate RhoA and inactivate Rac1, respectively, during axon guidance [46,47]. A recent study showed that similar to ephexin1, α2-chimaerin is enriched at postsynaptic sites and is required for EphA-dependent dendritic spine retraction in mouse hippocampal slices [45,48]. Overexpression of α2-chimaerin shrinks dendritic spines, recapitulating the phenotype observed during EphA4 overexpression. Thus, EphA4 may mediate dendritic spine

Figure 3



Distinct ephrin–Eph signaling at excitatory synapses modulates the enlargement or shrinkage of dendritic spines. Ephrin-dependent EphB stimulates different guanine nucleotide exchange factors (GEFs) at the dendritic spines during spine enlargement. The dynamic control of Rho GTPase signaling is critical for the structural plasticity. EphA4 is suggested to enhance RhoA activation through the concerted regulation of GEF and GTPase-activating protein (GAP) activity.

retraction through the coordinated action of ephexin1 and α2-chimaerin. Therefore, the coordinated regulation of GEF/GAP complexes is required for the precise control of synaptic Rho GTPase signaling.

Alpha-melanocyte-stimulating hormone and melanocortin 4 receptor

Besides receptor tyrosine kinases, G-protein-coupled receptors (GPCRs) also play important roles in regulating synaptic morphogenesis and functions. The GPCR, melanocortin 4 receptor (MC4R), is activated by its endogenous ligand alpha-melanocyte-stimulating hormone (α-MSH), which is generated from the cleavage of pro-opiomelanocortin (POMC). While melanocortin signaling is well known to regulate food intake and energy balance, MC4R is prominently expressed in the postsynaptic regions of the mouse hippocampus [49]. MC4R activation by its agonist increases the number of dendritic spines in cultured hippocampal neurons. Furthermore, MC4R activation leads to the insertion of AMPA receptors into synapses and increases AMPA receptor-mediated synaptic transmission. While the detailed mechanisms underlying the action of MC4R are unclear, MC4R activation regulates spine morphology and synaptic function via Gs-adenylyl cyclase-protein kinase A (PKA) signaling. Indeed, PKA signaling may regulate dendritic spine morphology by enhancing the phosphorylation-dependent incorporation of AMPA receptor into synapses or through the phosphorylation of various actin regulators such as Tiam1, WAVE1, and RhoA [49]. We recently mapped the POMC circuit in the mouse hippocampus and found that the POMC neurons in the CA3 hippocampal region activate MC4R in the CA1 region in response to synaptic activity [50•]. Furthermore, deletion of MC4R in the CA1 region of the mouse hippocampus reduces dendritic spine volume, whereas peripheral administration of an MC4R agonist enhances structural and functional synaptic plasticity in the hippocampus.

Spine loss and dysfunction in AD

Abnormal spine morphology and functions are associated with neurological disorders including autism and AD. AD is characterized by cognitive decline, and its pathological hallmarks include beta-amyloid plaques, which mainly comprise amyloid-beta peptide (Aβ) and fibrillary tangles, which are intracellular aggregates of hyperphosphorylated Tau protein. While extensive dendritic spine loss is observed in AD patients, synapse reduction is the feature most closely correlated with the decline of memory and cognition [51,52]. A recent study suggests that the dendritic spine loss in engram neurons (a specific population of neurons that are active during memory encoding) is associated with the deficits of memory retrieval in early AD mouse models [53•]. Thus, restoring the dendritic

spines in these neurons may be an effective strategy for ameliorating the memory loss in early AD.

While the total Aβ plaque burden (*i.e.*, insoluble Aβ aggregates) is not associated with memory impairment in AD, it is believed that the soluble oligomeric form of Aβ is the major agent that triggers dendritic spine loss and cognitive deficits [54,55]. Aβ interacts with a wide range of cell-surface receptors at synapses, including neurotransmitter receptors (*e.g.*, α7 nicotinic acetylcholine receptors), GPCRs such as metabotropic glutamate receptor (mGluR5) and β2 adrenergic receptors, receptor tyrosine kinases including EphB2 and EphA4, prion protein, the Wnt receptor fizzled, and insulin receptors [56]. In particular, the action of Aβ can be mediated through the deregulation of the expression levels or activity of Eph receptors. Aβ binds to the extracellular domain of EphB2, causing the ubiquitin–proteasome-dependent degradation of the receptor [57]. Accordingly, increasing EphB2 expression in hippocampal neurons reverses the synaptic deficit in AD mouse models. On the other hand, Aβ administration leads to EphA4 overactivation in cultured hippocampal neurons. EphA4 activation leads to dendritic spine retraction and the proteasomal-dependent degradation of AMPA receptors [43–45], both of which are critical factors that contribute to the synaptic deficit in AD. While EphA4 is a synaptic target of Aβ [58], EphA also decreases the glutamate uptake in astrocytes through the ephrinA3-mediated reduction of glutamate transporters in astrocytes [59]. Thus, it would be of interest to examine whether impaired EphA4–ephrinA3 reverse signaling mediates synaptic deficits in AD through the accumulation of extracellular glutamate. We previously demonstrated that chronic elevation of synaptic activity stimulates EphA4 activation [43]; therefore, it is critical to determine whether the glutamate overflow deregulates spine morphology and hence negatively impacts synaptic functions through EphA4 signaling. It is noteworthy that blockade of EphA4 rescues the Aβ-induced spine defects and synaptic functions [58,60]. Thus, modulating the expression or activity of specific Ephs, which are the cell-surface receptors of Aβ [61•], may represent a novel approach for the treatment of AD.

Other than the receptor tyrosine kinases, GPCRs such as mGluR5 and β2 adrenergic receptor are the receptors of Aβ oligomers [62], indicating that GPCR signaling is involved in the pathogenesis of AD. Indeed, neuromodulation through GPCRs is critical for shaping dendritic spines and circuits. Mapping of the functional POMC/MC4R circuit in the mouse hippocampus [50•] suggests that the activation of postsynaptic MC4R by the presynaptic release of α-MSH is critical for hippocampal synaptic plasticity. Aβ treatment reduces POMC expression in acute hippocampal slices, and α-MSH level is decreased in the hippocampus of APP/PS1 mice, an AD transgenic mouse model. Together with the finding that α-MSH level is reduced in the cerebrospinal fluid of AD patients [63], these findings support the notion that hippocampal α-MSH–MC4R signaling is disrupted upon AD progression. Indeed, blockade of hippocampal POMC/MC4R, particularly removal of POMC cells in the CA3 region, which secrete α-MSH, causes the early development of synaptic plasticity impairment in AD transgenic mouse models [50•]. In contrast, activation of the POMC/MC4R circuit by exogenous administration of MC4R ligand reverses the defects in dendritic spine morphology and impairment of synaptic plasticity in the hippocampus in APP/PS1 mice. Thus, replenishment of the ligands or agonists of the candidate postsynaptic receptors may be an alternative approach for treating AD. Indeed, systemic administration of MC4R agonists into AD mouse models has been reported to exert beneficial effects in certain learning and memory tasks [64,65].

Conclusion and perspective

Structural synaptic plasticity in the hippocampus is functionally implicated in learning and memory. In this review, we discussed how multiple cell-surface receptors transduce extracellular signals to affect intracellular actin dynamics through the coordinated regulation of Rho GTPases during synaptic potentiation. Different cell-surface receptors may act on a single subfamily of Rho GTPases, or a single receptor may trigger the activation of multiple Rho GTPases. Understanding the precise spatiotemporal dynamics and coordination of receptor–Rho GTPase signaling will further elucidate how these receptors function in synaptic plasticity. Such knowledge may help to identify molecular targets for developing therapeutic strategies for AD.

Conflict of interest statement

Nothing declared.

Acknowledgements

We apologize to the researchers whose studies could not be discussed or cited because of space limitations. We thank Ka-Chun Lok for preparing the figures in this review and Dr. Wing Yu Fu and Dr. Kwok On Lai for critical reading and discussions. Work carried out in the laboratory of N.I. is supported by the Hong Kong Research Grants Council Theme-based Research Scheme (T13-607/12R), the National Key Basic Research Program of China (2013CB530900), the Area of Excellence Scheme of the University Grants Committee (AoE/M-604/16), the Research Grants Council of Hong Kong SAR (16149616, 16102715, and 16102815), Food and Health Bureau (02132976 and 0314476), the Innovation and Technology Fund for State Key Laboratory (ITCPT/17-9), and the SH Ho Foundation.

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