Progress in Neurobiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

The actin cytoskeleton in memory formation

Raphael Lamprecht [a,b,c,*]

[a] Sagol Department of Neurobiology and Department of Biology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel
[b] Center for Gene Manipulation in the Brain, University of Haifa, Haifa, Israel
[c] Center for Brain and Behavior, University of Haifa, Haifa, Israel

ARTICLE INFO

Article history:
Received 27 August 2013
Received in revised form 2 February 2014
Accepted 3 February 2014
Available online xxx

Keywords:
Learning and memory
Actin cytoskeleton
Actin regulatory proteins
Brain
Neurons

ABSTRACT

The ability to efficiently store memories in the brain is a fundamental process and its impairment is associated with multiple human mental disorders. Evidence indicates that long-term memory (LTM) formation involves alterations of synaptic efficacy produced by modifications in neural transmission and morphology. The actin cytoskeleton has been shown to be involved in these key neuronal processes by subserving events such as presynaptic vesicle movement, postsynaptic glutamate receptors trafficking and dendritic spines morphogenesis. Actin cytoskeleton dynamics and structure underlying such cellular events can be regulated by extracellular signals through its regulatory proteins. Recent findings show that the actin cytoskeleton and its regulatory proteins are needed for memory formation and extinction in different organisms throughout the phyla from invertebrates such as Caenorhabditis elegans and Drosophila to mammalians. The actin cytoskeleton and its regulatory proteins participate in the formation of various types of memories that are subserved by different neurons and brain regions. The actin cytoskeleton may therefore mediate between synaptic transmission during learning and long-term cellular alterations mandatory for memory formation.

Contents

Abbreviations: ABR, active BCR-related; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BCR, breakpoint cluster region; BLA, basolateral complex of the amygdala; C. elegans, Caenorhabditis elegans; CNF1, cytotoxic necrotizing factor 1; CPP, (±)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid; CTA, conditioned taste aversion; DAB, 1,4-dideoxy-1,4-imino-D-arabinitol; DHPG, (S)-3,5-dihydroxyphenylglycine; fEPSP, field excitatory postsynaptic potential; GAPs, GTPases activating proteins; GEFs, guanine nucleotide exchange factors; IA, inhibitory avoidance; IP3K-A, inositol 1,4,5-trisphosphate 3-kinase A; IrL, infralimbic cortex; IRSp53, insulin receptor tyrosine kinase substrate of 53 kDa; JPK, jasplakinolide; LIMK, LIM-motif containing protein kinase; LMT, mossy fiber terminal; LTD, long-term depression; LTM, long-term memory; LTP, long-term potentiation; MLCK, myosin light chain kinase; miRNA, microRNA; mTORC2, mammalian target of rapamycin (mTOR) complex 2; NMDA, N-methyl-D-aspartate; PAK, p21-activated kinase; PKA, protein kinase A; PKC, protein kinase C; PPF, paired-pulse facilitation; PSD, postsynaptic density; RLC, myosin regulatory light chain; ROCK, rho-associated kinase; RP, reserve pool; RRP, readily releasable pool; STM, short-term fear memory; WAVE, Wiskott–Aldrich syndrome protein family.

* Correspondence address: Sagol Department of Neurobiology, University of Haifa, Haifa 31905, Israel. Tel.: +972 4 8288786; fax: +972 4 8288763.
E-mail address: rlamp@research.haifa.ac.il

http://dx.doi.org/10.1016/j.pneurobio.2014.02.001
0301-0082/

1. Introduction

Ample evidence indicates that long-term memory (LTM) formation involves alterations of synaptic efficacy (Konorski, 1948; Hebb, 1949; Dudai, 1989; Bliss and Collingridge, 1993; Martin et al., 2000; Tsien, 2000; Kandel, 2001; Lamprecht and LeDoux, 2004). These changes can be mediated by modifying synaptic release of transmitters or synaptic responses to these transmitters. In addition, changes in neuronal morphology regulating synaptic contacts and signal transduction near the synapse can affect synaptic efficacy. A major challenge is to identify molecules involved in initiating and maintaining synaptic alterations and memory formation. Actin is a most attractive candidate to play a central role in memory formation as it is responsive to synaptic signaling, such as triggered during learning, and consequently may mediate cellular events that underlie changes in synaptic efficacy, such as synaptic transmission and morphology.

Actin cytoskeleton is involved in many pivotal cellular processes including cellular morphogenesis, motility, division, and intracellular transport. Actin exists in two forms in cells, either as a globular monomer (G-actin) or following head-to-tail interaction as a polymer to form filamentous F-actin. Actin dynamics and the structure of F-actin network are closely regulated by actin regulatory proteins (Luo, 2000; Dillon and Goda, 2005). These actin cytoskeleton-regulatory proteins mediate between intrinsic and extrinsic cellular signals and actin-dependent cellular functions. Thus, by forming such elaborate network of actin filaments receptive to regulatory signals, actin mediates a large variety of cellular functions from supporting cellular morphology to providing contractile forces needed for cellular activities including cell division and transport of vesicles. Actin monomers and filaments are abundant in presynapses and postsynapses and act to regulate central neuronal processes such as changes in synaptic transmission and morphology (Luo, 2002; Dillon and Goda, 2005; Cingolani and Goda, 2008; Nelson et al., 2013). Changes in synaptic transmission and neuronal morphology are involved in the process of memory formation (Lamprecht and LeDoux, 2004).

This review is focused on the roles of the actin cytoskeleton in memory formation. As mentioned above, actin is involved in neuronal transmission and morphogenesis and in synaptic plasticity (Luo, 2002; Dillon and Goda, 2005; Cingolani and Goda, 2008) neuronal processes that have been shown to be involved in memory formation. These findings beg the questions: is the actin cytoskeleton needed for long-term memory formation? If so, which cellular mechanisms are modulated by the actin cytoskeleton and how they subserve memory formation?

2. Actin and memory formation

Studies have shown that the actin cytoskeleton is needed for memory formation. Actin was shown to be needed for the creation of memory in animals across the phyla and in various behavioral paradigms mediated by different neurons and brain regions. Interfering with actin rearrangements (e.g. inhibition of actin polymerization) at a particular time window during learning or afterwards impairs normal memory formation. Useful chemicals for interfering with the actin cytoskeleton rearrangements are latrunculin A that forms a nonpolymerizable 1:1 complex with G-actin to inhibit actin polymerization, cytochalasin D that caps the growing end of actin filaments and thus changes the polymerization and depolymerization rates of F-actin and phalloidin that binds to F-actin preventing its depolymerization and stabilizes it. For example, local application of actin polymerization inhibitors cytochalasin D or latrunculin A into the mushroom bodies of the honeybee 1 h before induction of long-term memory enhanced associative olfactory memory (Ganeshina et al., 2012). In rats, actin cytoskeleton is needed for spatial memory as intrahippocampal infusion of actin rearrangement inhibitor, latrunculin A, 15 min prior to initiation of the object placement task impaired object placement memory (Nelson et al., 2012). Actin cytoskeleton is also needed for aversive memories in rats as infusion of cytochalasin D or latrunculin A 4 h after conditioned taste aversion (CTA) into the insular cortex or prelimbic cortex, but not into the basolateral nucleus of the amygdala, impaired CTA LTM tested 72 h post-conditioning (Bi et al., 2010). Bilateral microinjection of latrunculin A into the amygdala 10 min before pairing with morphine withdrawal and infusion of latrunculin A into the dorsal hippocampus immediately after pairing significantly impaired conditioned place aversion (CPA) memory (Hou et al., 2009). Methamphetamine-associated memory in amygdala is disrupted by actin depolymerization (Young et al., 2014). Actin rearrangements were also shown to be involved in fear memory formation. Intra-hippocampal infusion of actin cytoskeleton assembly inhibitors (latrunculin A or cytochalasin D) in mouse impaired the consolidation of contextual fear memory (Fischer et al., 2004) and microinfusion of cytochalasin D into rat LA immediately before fear conditioning training interfered with the formation of

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

long-term fear memory (LTM) but not short-term fear memory (STM; Mantzur et al., 2009). Furthermore, microinfusion of cytochalasin D into rat LA immediately after fear conditioning dampened LTM. Cytochalasin D had no effect on fear conditioning memory retrieval when injected immediately before LTM test. Rehberg et al. (2010) showed that auditory cued but not contextual fear memory was disrupted, when the actin depolymerization inhibitor phalloidin was injected into basolateral complex of the amygdala (BLA) 6 h after conditioning. Re-consolidation of memory is also dependent on regulation of actin polymerization (Rehberg et al., 2010).

Actin cytoskeleton is also involved in memory extinction. Extinction is the decline in the frequency or intensity of a conditioned response when the stimulus that served as the conditioning stimulus is presented in the absence of the reinforcement (Pavlov, 1927). It does not reflect forgetting, but a process of relearning of a new association of the conditioned stimulus with the absence of the original reinforcer (e.g. Bouton, 1994; Rescorla, 1996). Conditioned fear responses to a tone or context paired with footshock rapidly extinguish when the tone or context are presented in the absence of the shock. Microinjection of latrunculin A or cytochalasin D into the hippocampus impaired the extinction of contextual fear memory (Fischer et al., 2004). Microinjection of cytochalasin D into the BLA or CA1 was shown to impair the return of fear after reconditioning at the last extinction session showing that actin polymerization is also required for reconditioning (Motanis and Maroun, 2012).

In summary, the aforementioned studies indicate that actin cytoskeleton is needed for memory formation and extinction in various organisms across the phyla. Actin cytoskeletal is needed for the formation of different types of memories and in different brain areas. It is therefore possible that similar cellular events, subserved by the actin cytoskeleton, occur following different learning paradigms and are needed for memory formation. Such events could include alteration in neuronal morphology such as changes in dendritic spines (referred as spines in the review below) or alteration in synaptic efficacy such as changes in amount of postsynaptic glutamate receptors known to be mediated by actin cytoskeleton (see below, table and Fig. 2). Importantly, studies provide evidence that interfering with actin dynamics that affect memory formation has no effect on normal synaptic transmission. For example, actin dynamics inhibitor in LA affects LTM formation but not fear memory retrieval (Mantzur et al., 2009) which requires synaptic transmission (e.g. Muller et al., 1997).

3. The roles of actin regulatory proteins in memory

How does neuronal activation during learning lead to alterations in actin cytoskeleton required for memory formation? Actin cytoskeleton polymerization, depolymerization and branching are closely controlled by regulatory proteins (Luo, 2000). Other actin-mediated function such as intracellular transport and contractility are also mediated by actin-binding proteins (Kamm and Stull, 2001; Somlyo and Somlyo, 2003). These regulatory proteins (Fig.. 1) can mediate actin involvement in memory formation as they are

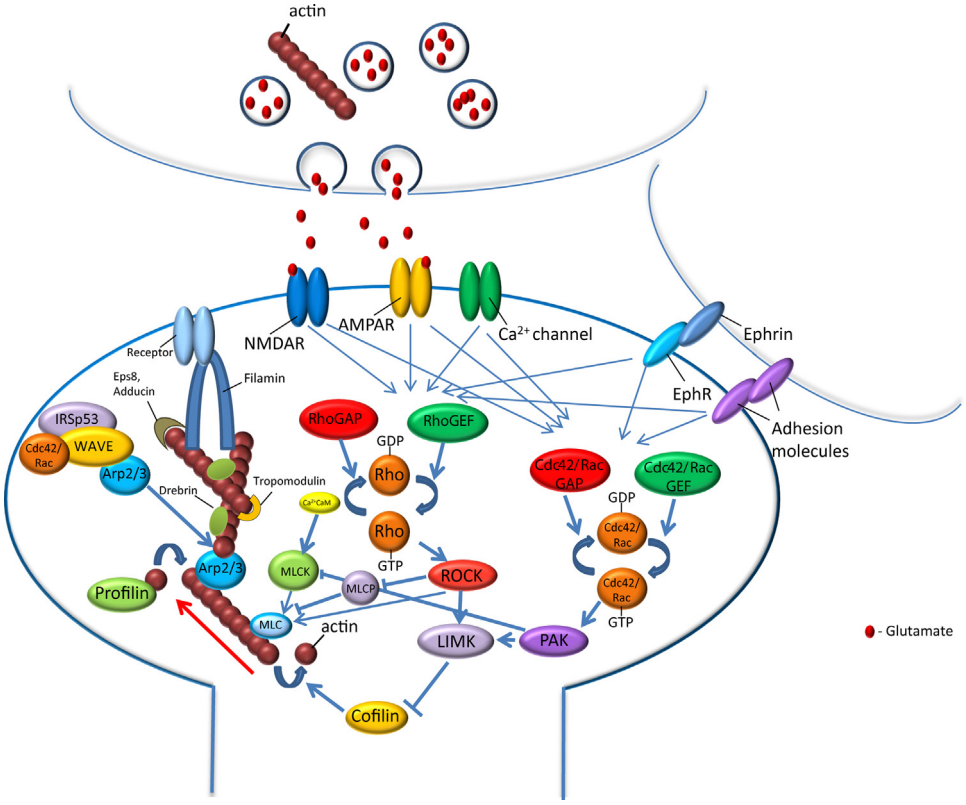

Fig. 1. Actin cytoskeleton and its regulatory proteins are involved in memory formation. Evidence shows that memory formation depends on the activation of glutamate receptors, calcium channels, receptors tyrosine kinases such as Eph receptors and adhesion molecules. Activation of these receptors and channels during or after learning may lead to regulation of intracellular signaling cascades that affect actin dynamics and structure and consequently cellular processes such as neuronal morphogenesis. Among these regulated molecules are the Rho, Rac, and Cdc42 GTPases and their effectors and actin-binding proteins such as profilin, Arp2/3, Eps8, Adducin, drebrin, Filamin and Tropomodulin shown to regulate actin polymerization, elongation, stabilization and branching. Of note is the fact that while actin regulatory protein activation may lead to regulation of similar effectors their effects on cellular function may be different. This may be due to different spatiotemporal regulation of these regulatory proteins. This figure illustrates the tight regulation of actin cytoskeleton needed for synaptic plasticity and memory formation. AMPAR – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CaM – calmodulin; IRSp53 – insulin receptor tyrosine kinase substrate of 53 kDa; LIMK – LIM-kinase; MLC – myosin light chain; MLCK – myosin light chain kinase; MLCP – myosin light chain phosphatase; NMDAR, N-methyl-D-aspartate receptor; PAK, p21-activated kinase; ROCK – rho-associated kinase; WAVE – Wiskott–Aldrich syndrome protein family.

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

functionally linked with synaptic receptors that participate in memory formation such as the glutamate receptors, Eph receptors, and adhesion molecules such as cadherin (Gerlai et al., 1999; Rodrigues et al., 2004; Schrick et al., 2007; Maguschak and Ressler, 2008; Savelieva et al., 2008). For example, actin dynamics in spines are inhibited by activation of either α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) or N-methyl-D-aspartate (NMDA) glutamate receptors (Fischer et al., 2000). Moreover, activation of either receptor inhibited actin-based protrusive activity from spine head. In addition, several actin regulatory proteins, such as members of the Rho GTPase family, are activated by glutamate receptor to regulate neuronal morphogenesis. For example, studies are available suggesting that RhoA mediates the promotion of normal dendritic arbor development by NMDA receptor activation (Li et al., 2000), and recruitment and activation of RhoA underlies spines morphology in a glutamate receptor-dependent manner (Schubert et al., 2006). Two-photon glutamate uncaging leads to long-term volume increase of single spine and to rapid activation of RhoA and Cdc42 in stimulated spine (Murakoshi et al., 2011). Moreover, NMDA or its downstream signaling pathways stimulation may lead to regulation of Rho or Rac GTPases activity (e.g., Tejada-Simon et al., 2006; Nakazawa et al., 2008; Saneyoshi et al., 2008). Eph receptors are also regulators of the Rho/Rac/Cdc42 GTPase proteins and affect actin dynamics and neuronal morphology (Shamah et al., 2001; Irie and Yamaguchi, 2002; Penzes et al., 2003; Egea and Klein, 2007; Klein, 2009). Adhesion molecules may regulate Rho/Rac/Cdc42 GTPase proteins to affect actin cytoskeleton (e.g. Brusés, 2006). Thus, synaptic molecules such as receptors and adhesion molecules activated during learning may affect actin-regulatory proteins leading to changes in actin cytoskeleton that subserve memory formation. The following sections will describe the roles of actin regulatory proteins in memory formation.

3.1. The roles of Rho GTPases signaling pathways in memory formation

3.1.1. Rho GTPase family GAPs and GEFs in memory

The Rho GTPase proteins (Rho/Rac/Cdc42) have been shown be activated by extraneuronal stimuli such as neurotransmission and adhesion (e.g. Luo, 2002; Dillon and Goda, 2005; Newey et al., 2005; Heasman and Ridley, 2008; Hall and Lalli, 2010; Tolias et al., 2011). Activation of Rho GTPases can alter actin cytoskeleton dynamics and structure (e.g. Luo, 2002; Dillon and Goda, 2005; Newey et al., 2005; Heasman and Ridley, 2008; Hall and Lalli, 2010). These molecules are also involved in memory formation (see below). Proteins that transduce signals from extra and intracellular signals to regulate the Rho GTPAses activity are the Guanine nucleotide exchange factors (GEFs) that activate monomeric GTPases by stimulating the release of guanosine diphosphate (GDP) to allow binding of guanosine triphosphate (GTP) and the Rho GTPase family activating proteins (GAPs) that bind to activated G proteins and stimulate their GTPase activity, with the result of terminating their signaling.

RhoGAP and RhoGEF families were shown to be activated by extracellular signaling including neurotransmitters and adhesion molecules in neurons. For example, NMDA receptor activation in pyramidal neurons leads to phosphorylation of the guanine-nucleotide exchange factor (GEF) kalirin-7, regulating its GEF activity (Xie et al., 2007). Kalirin could also be regulated by receptors that are intimately involved in neuronal morphogenesis such as EphB2 receptors (Penzes et al., 2003). The activation of the EphB receptor induces translocation of kalirin to synapses and activation of Rac1 and its effector p21-activated kinase (PAK). The activation of RhoGAPs and RhoGEFs may lead to alteration in neuronal processes such as morphogenesis. For example, kalirin expression and spine localization are required for activity-dependent spine enlargement and enhancement of AMPAR-mediated synaptic transmission (Xie et al., 2007). Thus, RhoGAPs and RhoGEFs could serve as cellular signaling mediators that couple extracellular stimuli during learning to Rho GTPases and actin cytoskeleton rearrangements subserving neuronal functions needed for memory formation. Studies below provide evidence that RhoGAP and RhoGEF are involved in memory formation.

The p190 RhoGAP is implicated in memory formation. P190 RhoGAP is a major substrate of the tyrosine kinase Src in the brain, and its phosphorylation by this kinase facilitates its interaction with p120 RasGAP and inhibits its RhoA-GAP and GTP-binding activities (Roof et al., 2000). P190 RhoGAP is intimately involved in brain development. P190 RhoGAP mutant mice exhibit neural developmental defects such as abnormalities in forebrain hemisphere fusion and neural tube closure and aberrations in axon outgrowth, guidance and fasciculation (Brouns et al., 2000; Brouns et al., 2001). P190 RhoGAP knockout in Drosophila causes retraction of axonal branches (Billuart et al., 2001). Importantly, evidence is available that p190 RhoGAP is involved in mediating actin reorganization. Specifically, in p190 RhoGAP mutant mice, polymerized actin accumulates extensively in cells of the neural tube floor, suggesting that p190 RhoGAP plays a role in regulating actin assembly (Brouns et al., 2000). P190 RhoGAP is involved in fear memory formation. Following fear conditioning, the tyrosine phosphorylated p190 RhoGAP becomes associated with a molecular complex in LA that includes the adaptor molecule GRB2 (Lamprecht et al., 2002). In addition, studies have shown that p190 RhoGAP may mediate Ptprz protein activities needed for memory formation. Ptprz is a receptor-type protein tyrosine phosphatase expressed in the brain (Nishiwaki et al., 1998). Ptprz selectively dephosphorylates pY1105 of p190 RhoGAP *in vitro*, and the tyrosine phosphorylation at Y1105 controls p190 RhoGAP activity *in vivo* (Tamura et al., 2006). Ptprz-deficient mice exhibit an age-dependent impairment of Morris water maze learning and impairments in contextual fear memory (Niisato et al., 2005; Tamura et al., 2006). Interestingly the authors found that p190 RhoGAP phosphorylation is decreased 1 h after the conditioning in the hippocampus of wild-type mice, but not of Ptprz-deficient mice.

Oligophrenin1 is a RhoGAP protein that inhibits RhoA, Rac1, and Cdc42 (Fauchereau et al., 2003; Govek et al., 2004). Oligophrenin-1 is expressed in the developing and adult brain, and present in neurons and glial cells where it colocalizes with F-actin (Fauchereau et al., 2003). In neurons oligophrenin-1 is found in pre- and post-synapse. Loss of oligophrenin-1 in knockout mice leads to immaturity of spines in the adult CA1 hippocampus (Khelfaoui et al., 2007). Long-term potentiation (LTP) and mGluR-dependant long-term depression are normal in the CA1 hippocampal area of oligophrenin-1 KO, whereas paired-pulse facilitation is reduced suggesting alteration in presynaptic processes involved in the release of neurotransmitters. Oligophrenin-1 KO mice are impaired in Morris water maze spatial learning (Khelfaoui et al., 2007).

Breakpoint cluster region (BCR) and active BCR-related (ABR) show RacGAP activities both *in vitro* and *in vivo* (Diekmann et al., 1991; Heisterkamp et al., 1993; Tan et al., 1993; Chuang et al., 1995; Voncken et al., 1995; Kaartinen et al., 2001; Cho et al., 2007). BCR or ABR KO induces a small increase in spine density without affecting excitatory synaptic transmission (Oh et al., 2010). Long term potentiation maintenance, but not induction, is impaired in BCR−/− or ABR−/− mice whereas long-term depression is normal (Oh et al., 2010). The BCR−/− and ABR−/− mice are impaired in Morris water maze and long-term object recognition memory (Oh et al., 2010).

The RacGAP, WRP, is thought to regulate central functions of synapse development and function and may be linked to mental

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

retardation in humans (Endris et al., 2002). The loss of WRP *in vivo* and *in vitro* leads to reduction in spines density. *In vivo* the loss is primarily of mushroom-shaped spines (Carlson et al., 2011). The loss of WRP led to impairments in long-term novel object recognition, water maze and passive avoidance memory (Carlson et al., 2011).

KALRN gene encodes for the kalirin Rac-GEF and can produce functionally distinct isoforms in a tissue-specific and developmentally regulated manner (McPherson et al., 2004). It was shown that kalirin can activate Rac1 and alter actin dynamics (e.g. Penzes et al., 2000). KALRN-deficient mice exhibit reduced cortical glutamatergic transmission, show brain region-dependent reductions in spine density and impairment in memory as assessed by Morris water maze and spontaneous alternation task in the Y-maze paradigm (Cahill et al., 2009; Vanleeuwen and Penzes, 2012). Kalirin-7 was shown to be involved in neuronal morphogenesis (Penzes et al., 2001). Knockout of Kalirin-7 in mice leads to decreased hippocampal spine density (Ma et al., 2008). Furthermore, in the KO mice early stages of cortical excitatory synaptic development proceeded normally with decreased excitatory synapses apparent after 21 days. These mice were impaired in short- and long-term passive avoidance conditioning and exhibited normal learning in radial arm maze and object recognition tasks. Thus, regulation of synaptic transmission and spines morphology by kalirin may be important for cognition. Another study shows that Kalirin KO mice were impaired in fear responses to the context when tested 45 min, 24 h and 48 h after contextual fear conditioning indicating an impaired ability of animals to acquire and consolidate new contextual fear memories (Xie et al., 2011). Mice were also impaired in cued fear conditioning where they associated sound with footshock. Mice were impaired in the 45 min and test 24 h tests but not in the 48 h test indicating that the mice are impaired in acquisition and early consolidation but not in latent onset of consolidation of cued fear conditioning memory.

Tiam1, a RacGEF, may also be involved in memory formation as phosphorylation of TrkB receptor, needed for memory formation, is required for its interaction with Tiam1 and with Rac1 activation during activity dependent spine remodeling (Lai et al., 2012). Tiam1 also binds to and functions downstream of the NMDA receptor (Tolias et al., 2005).

3.1.2. Rho GTPase family and memory

As described above Rho GTPase family GAPs and GEFs are involved in memory formation. These proteins regulate Rho GTPases and the question that arises is whether Rho GTPases are involved in memory formation? Indeed, several studies have provided compelling evidence for such a role. In Drosophila inhibition of Rac GTPase activity leads to slower decay of Pavlovian olfactory aversive conditioning memory, prolonging it from a few hours to more than one day, and to blockade of interference-induced forgetting. Conversely, increase in Rac GTPase activity in mushroom body neurons accelerates memory decay (Shuai et al., 2010). Rac activity triggers downstream activation of PAK and LIMK (LIM kinase), which in turn phosphorylates cofilin and inhibits its actin depolymerization activity (see below and Arber et al., 1998; Yang et al., 1998; Edwards et al., 1999). In Drosophila, hyperactivation of cofilin gives rise to the same phenotype as seen with Rac inhibition (Shuai et al., 2010). Thus, hyperactivation of cofilin following Rac inhibition may facilitate actin depolymerization and memory decay. Expression of a dominant-negative form of Drosophila Rac1, Drac1(N17) throughout the adult brain enhances the learning of Pavlovian trace conditioning of odor avoidance response compared with the two parental controls but leaves simultaneous conditioning unaffected (Shuai et al., 2011).

In rats microinjections of the Rac GTPase inhibitor NSC23766 into the nucleus accumbens (NAc) core but not shell, basolateral (BLA), or central amygdala (CeA) after each cocaine-conditioning session inhibited the consolidation of cocaine-induced long-term conditioned place preference (CPP) memory (Ding et al., 2013). Microinjection of NSC23766 into the BLA but not CeA, NAc core, or NAc shell disrupted the reconsolidation of cocaine-induced CPP.

Diana et al. (2007) have shown that the cytotoxic necrotizing factor 1 (CNF1) injected intracerebroventricular (i.c.v.) leads to activation of cerebral RhoA and Rac1, to rearrangement of cerebral actin cytoskeleton as shown by an increase in F-actin and to enhanced hippocampal neurotransmission and synaptic plasticity. Microinjection of CNF1 led to enhancement of long-term contextual fear conditioning memory as tested 1 and 10 days after training. Cued fear conditioning to a tone was not different 1 day after training but was enhanced 10 days afterwards. Mice showed an improvement of Morris water maze performance. The effects persisted for weeks. In addition, CNF1 intracerebroventricularly improved object recognition memory in both C57BL/6J and CD1 mice (Borrelli et al., 2013). The improvement is long lasting and was observed weeks after treatment. CNF1 also enhanced working memory for object location/discrimination in mice (De Viti et al., 2010).

Postnatal conditional knockout of Rac1 leads to fewer synapses, but existing spines are larger than those in control hippocampal neurons (Haditsch et al., 2009). Loss of Rac1 impaired LTP in both CA1 and dentate gyrus. Rac1 mutants are impaired in Morris water maze hippocampus-dependent spatial learning but not in long-term memory. The Rac1 deficient mice are impaired in working/episodic-like memory as tested in the "delayed matching-to-place" (DMP) version of the Morris water maze.

The Rac3 isoform is involved in behavioral flexibility. Rac3 knockout mice do not show defects in spatial reference memory assessed by water maze task but are different from wild type mice in the reversal phase showing difficulties to locate the new platform position indicating on a reduced behavioral flexibility to novel situations (Corbetta et al., 2008).

Rac-1 pathway is also involved in memory extinction. Mice injected with a Rac-1 inhibitor (NSC23760) intracerebroventricular immediately after each day of the contextual fear memory extinction days 1–3 showed facilitated extinction. Similar results were obtained by intrahippocampal injections (Sananbenesi et al., 2007).

Rac GTPase can be engaged in various intracellular pathways to affect memory. For example, in a recent study it was shown that Rictor (rapamycin-insensitive companion of mTOR) deficient mice are impaired in both long-term memory (LTM) and the late phase of hippocampal long-term potentiation (L-LTP) and that Rac1-GTPase signaling and actin may be involved in mediating this process (Huang et al., 2013). This study revealed that conditional deletion of Rictor in the postnatal murine forebrain greatly reduced mammalian target of rapamycin (mTOR) complex 2 (mTORC2) activity and impaired both long-term memory (LTM) and hippocampal L-LTP (Huang et al., 2013). Rictor fb-KO mice were impaired in long- but not short-term contextual and auditory fear memory. Rictor fb-KO mice were also impaired in spatial LTM as tested in the Morris water maze, where mice use visual cues to find a hidden platform. Several observations suggested that the phenotype observed in the Rictor KO mice engages alterations in actin polymerization. First, spine density in CA1 pyramidal neurons was reduced in Rictor fb-KO mice. Second, Rac1 GTPase activity and the phosphorylation of PAK and cofilin were reduced in CA1 neurons of Rictor fb-KO mice. Third, the ratio of polymerized F-actin to G-actin monomers, which indicates on the balance between actin polymerization and depolymerization, was reduced in CA1 of Rictor fb-KO mice. Fourth, microinjection of jasplakinolide (JPK), a compound which directly promotes actin polymerization, into the CA1 region improved contextual fear LTM in Rictor fb-KO mice indicating that actin dynamics account at least

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

to some extent for the impairment of LTM in these mice. JPK also enhanced contextual fear LTM in wt mice when the mice were trained with a weak conditioning protocol.

Another example of Rac GTPase possible involvement in memory formation is through its interaction with the inositol 1,4,5-trisphosphate 3-kinase A (IP3K-A) pathway. Neural activation leads to binding of IP3K-A, a brain-specific molecule that is enriched in spines (Mailleux et al., 1991), to activated Rac1 and to its recruitment to the actin cytoskeleton in the postsynaptic area leading to spine formation through actin dynamics downstream of Rac signaling (Kim et al., 2009a). IP3K-A knock-out mice exhibited impairments in synaptic accumulation of PAK1 caused by LTP-inducing stimulation and reduction in the reorganization of actin cytoskeleton in dentate gyrus synapses. In addition, IP3K-A knock-out mice showed deficits in synaptic plasticity in perforant path and in spatial memory using the radial arm maze test. Translocation of Rac and its activation was also shown to be increased in the hippocampus following contextual fear conditioning in mice in an NMDA-depended manner (Martinez et al., 2007).

Cumulatively, the above observations show that RhoGAP and RhoGEF families and their downstream affectors the Rho GTPase family of proteins, that affect the actin cytoskeleton, are involve in memory formation. The findings that the same protein (e.g. Kalirin) affects different memories suggests that similar cellular changes occur in different brain regions and following various types of learning. The observation that different proteins, sometime with opposite effects (e.g. RacGAP and RacGEF in water maze) are involved in the same memory formation is not necessarily contradictory as the proteins may be activated in different microcellular regions and time points. Regular genetic and pharmacological manipulations have an insufficient spatiotemporal resolution to be able to differentiate between such events.

3.1.3. Rho GTPases regulated pathways in memory

Rho GTPase family exerts their effects on actin dynamics by regulating downstream effectors (Luo, 2000; Fig.. 1). A major direct effector of Rho GTPase is the Rho-associated kinase (ROCK; Riento and Ridley, 2003; Amano et al., 2010). ROCK phosphorylates a number of proteins involved in regulating actin cytoskeleton including myosin light chain phosphatase and LIMK. Phosphorylation of myosin light chain or of myosin light chain phosphatase has an immediate impact on actin contractility (Kamm and Stull, 2001; Somlyo and Somlyo, 2003). LIMK exerts its effect on actin polymerization by phosphorylating and inactivating the actin depolymerization factor (ADF)/cofilin (Arber et al., 1998; Yang et al., 1998; Sumi et al., 1999). Activation of LIMK by ROCK has been associated with phosphoregulation of ADF/cofilin (Maekawa et al., 1999). Cofilin plays an essential role in regulating actin filament dynamics and reorganization also by stimulating the severance and depolymerization of actin filaments (Bamburg and Bernstein, 2008). Rac GTPase and Cdc42 activate p21 activated kinase1 (PAK1), which in turn activates LIMK (Edwards et al., 1999) and therefore can affect actin dynamics (Bokoch, 2003). The following sections address the roles of Rho GTPases downstream effectors in memory formation and extinction.

3.1.3.1. Rho-associated kinase (ROCK) and memory. Rho-associated kinase was shown to be involved in memory formation. Inhibition of ROCK in lateral amygdala (LA) impaired the formation of long- but not short-term fear memory formation (Lamprecht et al., 2002). Intra-LA infusions of the ROCK inhibitor Y-27632 impaired fear conditioning-induced expression of pre- and post-synaptic proteins GluR1, synapsin and synaptophysin in the LA (Ota et al., 2010). The investigators suggest that changes in the actin cytoskeleton induced by the Rho/ROCK signaling pathway may be responsible for the pre- and postsynaptic changes observed at the LA synapse following fear conditioning. ROCK inhibition prior to fear conditioning training attenuated fear memory and neuroxin splicing repressions in hippocampus (Rozic et al., 2011). Microinjection of ROCK inhibitor into the gustatory cortex impaired long-term CTA memory formation but not retrieval, relearning or incidental taste learning (Sweetat et al., 2012). Post training intrahippocampal infusion of Y-27632 impairs long-term Morris water maze memory (Dash et al., 2004).

3.1.3.2. p21 activated kinase (PAK) and memory formation and extinction. PAK is involved in neuronal morphogenesis and memory formation and extinction. Cortical neurons in forebrain-specific dnPAK transgenic mice exhibited fewer spines and an increased proportion of larger synapses (Hayashi et al., 2004). These mice were impaired in bidirectional synaptic modifiability (enhanced LTP and reduced LTD) in the cortex. The mutant mice were normal in acquisition of Morris water maze but impaired in this task when tested 21 days (but not 1 day) after training indicating that consolidation/retention of this memory is impaired in the transgenic mice. Similarly, animals were normal in short-term contextual fear conditioning memory but impaired in long-term memory when compared to controls. Pak5−/− Pak6−/− double KO acquired the correct avoidance response in the active avoidance component of the T-maze at a much slower rate than the wild type mice and performed more poorly in most of the sessions (Nekrasova et al., 2008). Pak5−/−;Pak6−/− mice performed worse than wild type mice in passive avoidance task. Anxiety levels are normal in the Pak5−/−;Pak6−/− mice but they suffer from deficits in locomotor activity and strength. Although some behavioral differences were seen in the Pak5 and Pak6 single KO mice, the double KO mice showed the greatest changes in locomotion and learning and memory (Furnari et al., 2013).

PAK-1 is also involved in memory extinction. Mice that were trained for contextual fear conditioning and were microinjected 24 h later with HSV–dnPAK-1 into the hippocampus showed a significant impairment in extinction when compared with HSV-GFP control group (Sananbenesi et al., 2007). These data indicate that inhibition of PAK-1 activity impairs extinction.

3.1.3.3. LIMK and memory. ROCK and PAK can regulate actin cytoskeleton via signaling molecules such as LIMK that affects actin dynamics. The normal distribution of actin in hippocampal neurons (showing higher level in the spines compared to dendrites) was disrupted in LIMK-1 knockout neurons (the spine intensity of actin staining is weak and not significantly higher than that of dendritic areas) indicating that LIMK-1 is critical for a high level of expression of actin filaments in the spines. Furthermore, in LIMK-1 KO neurons actin filaments accumulate abnormally along the dendrites (Meng et al., 2002). The knockout mice exhibited significant abnormalities in spine and axonal morphology. LTP induced by tetanic stimulations of 5 or 10 Hz in mice was impaired in the LIMK knockout slices but LTP induced by 50 or 100 Hz stimulation was clearly enhanced in the KO mice (Meng et al., 2002). The LIMK-1 knockout mice also showed enhanced cued fear conditioning LTM. These mice were tested also in spatial memory task the Morris water maze showing significant impairment in locating a submerged platform position when the platform was moved to the opposite quadrant during the learning reversal phase indicating of impairment in some aspects of spatial memory formation. These results indicate that the regulation of actin polymerization by the LIMK pathway is essential for normal fear and spatial memory formation.

3.1.3.4. Cofilin and memory. The LIMK effector cofilin regulates actin dynamics and is involved in memory formation. Mice in which n-cofilin was removed from principal neurons postnatally

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

(N-cofflx/flx,CaMKII-cre) were tested cellularly and behaviorally. A 50–60% increase in the F/G-actin ratio was detected in cortex and hippocampus synaptosomes of mutant mice compared to controls showing that n-cofilin is critical to maintain the equilibrium of synaptic F-actin and G-actin. The density of spines in CA1 pyramidal neurons of n-cofflx/flx,CaMKII-cre,Thy1-GFP mice was increased compared to control mice. The number of mushroom-shaped spines was higher in mutant mice and spine heads were also larger, but the number of filopodia-like spines was not altered. N-cofilin is shown to be important for synaptic plasticity (L-LTP or LTD) and for AMPAR mobility. N-cofflx/flx,CaMKII-cre mice are impaired in Morris water maze learning and in contextual and cued fear learning (Rust et al., 2010). N-cofflx/flx,CaMKII-cre mice performed worse when compared to controls in conditioned place preference reward learning. Short-term working memory and exploratory learning are shown to be n-cofilin independent.

Cofilin phosphorylation is altered by behavior. Rats trained in inhibitory avoidance (IA) exhibit an increase in phospho-cofilin (p-cofilin) 20 h after training in the hippocampus. This increase is dependent on astrocytic glycogenolysis as it is blocked by 1,4-dideoxy-1,4-imino-D-arabinitol (DAB), an inhibitor of glycogen phosphorylation, that also blocked long-term, but not short-term, IA memory (Suzuki et al., 2011). In another study rats were allowed to explore a compartmentalized environment for 30 min. Rats that explored the environment had 30% more spines with dense phosphorylated cofilin in hippocampal CA1 than did rats in the home-cage group. The increase in p-cofilin containing spines and behavioral evidence for memory of the explored environment were both eliminated by the NMDA receptor antagonist (±)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) (Fedulov et al., 2007). Object placement training resulted in increased hippocampal levels of p-cofilin (Nelson et al., 2012). Another study has shown that β-arrestin-2 plays a critical role in NMDA-induced changes of spines and synapses via translocation of active cofilin to spines (Pontrello et al., 2012). β-arrestin-2 KO are impaired in water maze learning.

Cofilin is also involved in memory extinction. The extinction of conditioned taste aversive (CTA) memory led to temporally enhanced ADF/cofilin activity in rat infralimbic cortex (IrL; Wang et al., 2013). Elevation of ADF/cofilin activity in the IrL facilitated CTA memory extinction whereas inhibition of ADF/cofilin activity impaired memory extinction. Cofilin activity was also needed for the regulation of AMPA receptor trafficking to the synapse. It was also shown that extinction training decreased LIMK1 activity while increasing Slingshot (SSH1) activity. Cofilin is mainly phosphorylated by LIMKs and dephosphorylated by Slingshot (SSH) phosphatase (Van Troys et al., 2008).

Taken together, the above observations show that disrupting proteins activities within the pathways from the synapse to cofilin (via ROCK or PAK) can affect actin cytoskeleton dynamics and memory formation and extinction. Thus, cumulatively these results implicate these pathways in memory formation (Fig.. 1).

3.2. Actin capping, crosslinking, stabilizing and elongating regulatory proteins and their roles in memory formation

3.2.1. WAVE scaffolding protein is involved in actin network formation and long-term memory

The WAVE isoforms (WAVE-1, WAVE-2 and WAVE-3) permit assembly of multiprotein complexes with proteins that can affect actin structure such as the Arp2/3 (see below and also Bear et al., 1998; Machesky and Insall, 1998; Volkmann et al., 2001; Rodal et al., 2005; Takenawa and Suetsugu, 2007; Pollitt and Insall, 2009). Rac signaling is also coordinated by the WAVE (Wiskott–Aldrich syndrome protein family)/Scar (suppressor of cAMP receptor) family of scaffolding proteins (Machesky and Insall, 1998). Loss of WAVE-1 affects both lamellipodial dynamics and the pattern of growth cone motility in a way that retards neurite extension (Soderling et al., 2007). In addition, loss of WAVE-1 leads to reduction in spine density. Null WAVE mice were impaired in LTP and LTD. Mice with WAVE mutation that leads to reduced WRP (a RacGAP) binding were impaired in hippocampal-dependent Morris water maze memory retention (Soderling et al., 2007). Impairments in mutant mice were also detected in novel-object recognition tests performed to assess hippocampal-independent nonspatial memory. In another study it was shown that targeted disruption of the WAVE-1 gene generated mice with reduced anxiety, sensorimotor retardation, and deficits in Morris water maze and novel-object recognition, but not passive avoidance, memory (Soderling et al., 2003).

3.2.2. Arp2/3 in actin branching, structural plasticity and memory

Arp2/3 is activated by neuronal WASP and WAVE1 proteins, downstream of Rho GTPase family members such as Cdc42 and Rac (Pollard, 2007; Rotty et al., 2013). It initiates branched filament polymerization to create actin meshworks (Mullins et al., 1998). The Arp2/3 may be involved in spine actin remodeling and is enriched in submembrane region surrounding the spine head (e.g. Rácz and Weinberg, 2008; Wegner et al., 2008; Nakamura et al., 2011; Lippi et al., 2011). Actin turnover defect in spines was detected following deletion of ArpC3, an essential Arp2/3 subunit (Kim et al., 2013). Furthermore, postnatal deletion of ArpC3 induces a progressive loss of spines *in vivo*. ArpC3 is also involved in structural plasticity and loss of ArpC3 prevents the maintenance of activity-induced enlarged spines. Interestingly activity-dependent spine shrinkage was normal in ArpC3 deleted neurons. Asymmetric spine structural plasticity in ArpC3 deleted neurons was shown to be followed by an accumulation of filopodia-like spines and such spines contained less PSD-95, fewer glutamate receptors and reduced downstream activation of CaMKII. ArpC3f/f:CamKIIα-Cre mice were assessed using Y-maze (working memory) and novel object recognition tests (episodic memory). In the Y-maze test the percentage of alternations was significantly decreased in the adult ArpC3f/f:CamKIIα-Cre mice indicating of impairment in working memory. In the novel object recognition test ArpC3f/f:CamKIIα-Cre mice were severely impaired in short-term, long-term and remote memory capabilities.

3.2.3. Insulin receptor tyrosine kinase substrate of 53 kDa (IRSp53) and memory

Insulin receptor tyrosine kinase substrate of 53 kDa (IRSp53) is an abundant protein in the postsynaptic density (PSD) that contains several domains for protein–protein interactions and regulates Rac-dependent lamellipodia formation through WAVE2-mediated regulation of Arp2/3 and F-actin polymerization (Miki et al., 2000; Nakagawa et al., 2003; Cheng et al., 2006; Suetsugu et al., 2006; Abou-Kheir et al., 2008). IRSp53 and the IRS-58 also regulates Cdc42-dependent filopodia formation via Mena and Eps8 (Miki et al., 2000; Govind et al., 2001; Krugmann et al., 2001; Disanza et al., 2006). NMDA receptor activation is needed for IRSp53 accumulation in spines and specifically in excitatory synapses (Hori et al., 2005). Furthermore, it was shown that actin cytoskeleton is involved in the NMDA receptor-mediated synaptic translocation of IRSp53 as NMDA stimulation did not lead to synaptic translocation of IRSp53 in neurons pretreated with latrunculin A. In addition, it was shown that the synaptic translocation of IRSp53 enhances the postsynaptic activity. The roles of IRSp53 in neuronal functions and memory were studied in knockout mice (Kim et al., 2009b). IRSp53 deficiency had no effect on spine density and ultrastructure, basal synaptic transmission, presynaptic release and evoked and spontaneous AMPA receptor-mediated synaptic transmission. However, IRSp53−/− mice

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

exhibited a reduced AMPA/NMDA ratio of excitatory transmission and enhanced NMDA receptor-mediated transmission and LTP. IRSp53−/− mice were impaired in Morris water maze and novel object recognition learning and memory.

3.2.4. Abi family of proteins in memory formation

Additional proteins that interact with WAVE are the Abi1 and Abi2 (Eden et al., 2002; Soderling et al., 2002). During passive avoidance training, wild-type, Abi2+/−, and Abi2−/− mice were equally likely to cross rapidly to the darkened chamber but when tested at 0.5, 1, or 24 h later, wild-type mice showed substantially longer latencies to cross to the dark chamber relative to Abi2+/− and Abi2−/− mice. This observation indicates that Abi2+/− and Abi2−/− mice are deficient in short- and long-term memory formation.

Taken together, the above findings show that proteins that bind to WAVE or WASP (see also profilin below) are involved in memory formation. It is therefore possible that a complex of proteins including the scaffolding proteins WAVE and WASP work in a coordinated manner to convert signals from protein–protein and membrane-protein interactions to actin polymerization to regulate actin dynamic in discrete neuronal locations (e.g. activated synapses) needed for neuronal changes such as spine morphogenesis that support memory formation.

3.2.5. Filamin, a F-actin cross linker protein, in memory formation

Filamins are large actin-binding proteins that stabilize actin webs by crosslinking F-actin and linking them to cellular membranes (Stossel et al., 2001). It was shown that abnormal expressions levels of cheerio, the Drosophila fly homolog of Filamin A, are associated with specific defects in LTM memory formation after Pavlovian olfactory learning (Bolduc et al., 2010).

3.2.6. EPS8, an actin capping protein, is involved in memory formation

Eps8 is involved in actin remodeling through actin barbed end capping and actin bundling activities (Disanza et al., 2004, 2006). In Eps8 KO mice a significantly higher number of presynaptic and postsynaptic puncta were detected in the hippocampus (Menna et al., 2013). The structural organization of the presynaptic compartment is not altered in Eps8 KO mice but there is a clear alteration in the morphology of spines, which appeared thinner and were significantly longer. The authors also show that actin-capping activity of Eps8 is required for proper mushroom-type spine formation. In addition, a significant increase in protrusions per unit length was detected on secondary branches of CA1 neuronal dendrites in the Eps8 KO. In addition, the study unveil that the capping activity of Eps8 is essential for LTP-mediated synapse formation and strengthening. Radial maze, novel object recognition, passive avoidance learning and memory are impaired in Eps8 knockout mice (Menna et al., 2013). Importantly, structural plasticity after learning is impaired in mutant mice trained for object recognition. These mice did not display any increase in spine number, which shown in wt mice 24 h after training in hippocampus.

3.2.7. Drebrin A, an actin stabilizing protein, in memory formation

Drebrin is an actin-binding protein enriched in spines (Hayashi et al., 1996; Aoki et al., 2005; Sekino et al., 2007) and is involved in stabilizing actin filaments through its effect on their inter-strand and intra-strand contacts (Mikati et al., 2013). Drebrin has several isoforms where drebrin E is an embryonic isoform and drebrin A is an adult isoform (reviewed in Sekino et al., 2007; Kojima et al., 2010). The isoform conversion is parallel with synapse maturation. Kojima et al. (2010) generated knockout mice in which a drebrin A-specific exon was deleted leading to a mouse (termed DAKO) expressing drebrin E instead of drebrin A. DAKO mice show no apparent abnormalities in their gross brain morphology and general behaviors. DAKO mice are however impaired in long-term contextual, but not auditory, fear conditioning memory.

3.2.8. Adducin, an actin filament barbed end capping protein, is needed for memory formation

Adducins cap and bundle actin filaments, and promote spectrin binding to actin filaments (Gardner and Bennett, 1987; Mische et al., 1987; Kuhlman et al., 1996). Calmodulin binding and phosphorylation by protein kinase A (PKA) and protein kinase C (PKC) can detach adducins from the barbed ends of filamentous actin (Matsuoka et al., 1996, 1998). The mammalian adducin family is encoded by three genes (α, β, and γ) with various splice variants (Suriyapperuma et al., 2000). Functional adducin is composed of heterodimers or heterotetramers of α/β or α/γ subunits (Dong et al., 1995; Hughes and Bennett, 1995). The roles of adducin in synaptic plasticity and memory were studied in several adducin mutant mice lines. Hippocampal CA1 short- and long-term synaptic plasticity is impaired in β-adducin knock-out mice (Rabenstein et al., 2005). Spines of the β-adducin knock-out mice appear normal. β-adducin knock-out animals were impaired in performance of both the Morris water maze memory and long-term cued and contextual fear conditioning memory tests compared with their wild-type littermates (Rabenstein et al., 2005). Mice lacking β-adducin fail to assemble new synapses upon enhanced plasticity (Bednarek and Caroni, 2011). Environmental enrichment leads to stable assembly of new synapses which is dependent on β-adducin, and disassembly of synapses engages β-adducin phosphorylation via PKC. In the absence of β-adducin, enrichment still cause an increase in spine structures, however the assembly of synapses at those spines is compromised. β-adducin was shown to be needed for environmental-enhanced long-term memory of contextual fear conditioning and novel object recognition. β-adducin was not needed for enrichment-enhancement of short-term memory. In another study it was shown that in Add2−/− mice average values of filopodia per large mossy fiber terminal (LMT) were similar to those in wild-type mice. Add2−/− mice exhibit enhanced putative release sites per core LMT upon fear conditioning but they were impaired in establishing higher numbers of filopodia upon fear conditioning. Add2−/− mice learned contextual fear conditioning but the memory was inexact and mice starts to generalized 1 day after learning. Similar findings were observed in Morris water maze and rotarod learning in Add2−/− mice (Ruediger et al., 2011). Thus, lack of learning-related feedforward inhibition connectivity growth in mice lacking β-adducin is correlated with poor accuracy of fear conditioning and Morris water maze memories. Another study show that β-adducin KO mice exhibit behavioral, motor coordination, learning deficits and are impaired in LTP and LTD (Porro et al., 2010). In the nematode Caenorhabditis elegans (C. elegans), the loss of α-adducin (add-1) selectively impaired short- and long-term aversive olfactory associative memory without causing acquisition, sensory, or motor deficits (Vukojevic et al., 2012). Moreover, it was found that the memory and consolidation of synaptic plasticity likely requires the barbed-end capping activity of ADD-1. Cytochalasin B, a well-characterized compound that inhibits actin polymerization by binding to the barbed end of actin filaments, rescued the memory defect of add-1 mutant worms. In humans, genetic variability of the ADD1 gene is associated with episodic memory performance in healthy young subjects. Human ADD1 expression in nematodes restored loss of *C. elegans* add-1 gene function (Vukojevic et al., 2012).

3.2.9. Tropomodulin, a pointed-end capping protein, is involved in memory formation

Tropomodulin binds to actin filament pointed end and prevents both elongation and depolymerization (Yamashiro et al., 2012). To

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

study the roles of Tropomodulin in behavior Cox et al. (2003) generated a Tropomodulin2 knockout mice (Tmod2lacZ−/−). Tmod2lacZ−/− mice exhibited no gross morphological or anatomical abnormalities, but were found to be hyperactive and with reduced sensorimotor gating. Tmod2lacZ−/− mice had enhanced LTP but no impairments in synaptic transmission or paired-pulse facilitation (PPF). Tropomodulin KO mice were impaired in contextual and cued conditioned fear and Morris water maze memory formation.

3.2.10. Spinophilin and Neubrin are actin binding proteins involved in memory formation

Neurabin (neurabin I) and spinophilin (neurabin II) are structurally similar cytoskeletal binding proteins that bind F-actin in the brain (Allen et al., 1997; Nakanishi et al., 1997; Satoh et al., 1998) and are implicated in regulation of neuronal morphology (e.g. Sarrouilhe et al., 2006). Neurabin KO mice showed a significant reduction in contextual fear memory 1 h, 1 day and 3 days after conditioning (Wu et al., 2008). Auditory fear memory was unaltered in neurabin KO mice. LTP in hippocampal CA1 neurons was significantly reduced whereas LTD was unaffected. Increased AMPA receptor but not NMDA receptor-mediated synaptic transmission was detected in neurabin KO mice. Spinophilin knockout mice were unable to learn a conditioned taste aversion (CTA) when sucrose or NaCl solutions were paired with a moderate dose of LiCl (Stafstrom-Davis et al., 2001).

3.2.11. Profilin, an actin monomer binding protein, in memory formation

Profilin is another actin cytoskeleton-regulatory protein involved in actin polymerization by funneling ATP-actin to the growing actin filaments (Witke, 2004). Profilin was shown to be translocated into spines in hippocampal neurons after neuronal stimulation, LTP or LTD (Ackermann and Matus, 2003; Neuhoff et al., 2005). Profilin movementis associated with the suppression of actin dynamics in the spine head and the stabilization of spine morphology. Fear conditioning in rats induces the translocation of profilin into spines in LA (Lamprecht et al., 2006a). Profilin-containing spines were shown to be larger compared to spines devoid of profilin. Increase in profilin-containing spines with enlarged PSDs could contribute to the enhancement of associatively induced synaptic responses in LA following fear learning. Mice with knockdown of one of the profilin isoforms, profilin2, are hyperactive and exhibit increased novelty-seeking behavior (Pilo Boyl et al., 2007). Freezing after fear conditioning is similar in control and knockout mice when number of freezings, but not time of freezing, is monitored during LTM test (Pilo Boyl et al., 2007).

Taken together the above observations indicate that the actin cytoskeleton is tightly regulated by multiple actin regulatory proteins and that interference with this regulation affects synaptic plasticity, structural plasticity and memory formation. The proteins described above controls actin dynamic, stability and structure to produce an appropriate cytoskeleton structure mediating morphology and transmission (see below). Actin can mediate other cellular functions such as contractility and cellular transport by serving as a platform for the motor protein myosin as described below.

3.3. The actin binding motor protein myosin in memory formation

Myosins are motor proteins that interact with actin filaments and hydrolyze ATP to produce movement and force (Kneussel and Wagner, 2013). This process allows myosins to drive the sliding of actin filaments, to produce tension on actin filaments and to advance along these filaments. As a consequence, myosins can regulate the structure and dynamics of the actin cytoskeleton and affect the localization and transport of cellular components.

It was shown that myosin and it regulatory proteins are involved in brain actin dynamics, synaptic plasticity and memory formation. Rex et al. (2010) showed that myosin IIb expression is involved in actin dynamics following the induction of LTP and is important for stabilization, but not induction, of early LTP. These investigators further demonstrated that injection of AAV to express MyH10 shRNAs or the specific inhibitor of myosin II ATPase activity, Blebbistatin (Blebb) (Kovacs et al., 2004; Limouze et al., 2004; Allingham et al., 2005) into the CA1 impaired long-term contextual fear conditioning memory. They also show that myosin II drives cytoskeletal changes needed for LTM formation that occur during, or very shortly after, the hippocampus-dependent associative training.

Infusion of blebb, directly into rats LA 30 min prior to cued fear conditioning impaired long-term, but not short-term, fear memory formation (Gavin et al., 2011). Intra-LA injections of recombinant adeno-associated virus (rAAV) particles expressing short hairpin RNA (shRNA) targeting Myosin IIB also impaired fear LTM.

Myosin light chain kinase (MLCK) is a calcium/calmodulin-dependent protein kinase that phosphorylates the myosin regulatory light chain (RLC), leading to contraction of the actomyosin filaments (Kamm and Stull, 2001; Somlyo and Somlyo, 2003). MLCK is involved in regulating cellular processes related to synaptic transmission, such as neurotransmitter release (Mochida et al., 1994; Ryan, 1999; Polo-Parada et al., 2001), NMDA receptor function (Lei et al., 2001) and potassium channel current modulation (Akasu et al., 1993). In addition, MLCK is involved in neural morphogenesis, including the regulation of growth cone motility (Gallo et al., 2002; Zhou et al., 2002) and dendritic branching (Ramakers et al., 2001). MLCK was shown to be involved in fear memory formation in LA. MLCK is present in cells throughout the LA and is localized to dendritic shafts and spines that are postsynaptic to the projections from the auditory thalamus to lateral nucleus of the amygdala, a pathway implicated in fear learning (Lamprecht et al., 2006b). Inhibition of MLCK in LA by microinjection of ML-7 (1-(5-iodonaphthalene-1-sulfonyl)-1H-hexahydro-1,4-diazepine hydrochloride), an inhibitor of MLCK, led to the enhancement of fear memory formation but had no effect on retrieval of fear memory (Lamprecht et al., 2006b). MLCK inhibition immediately following fear conditioning training had no effect on fear memory. The brevity time window of involvement of MLCK in fear conditioning is consonant with its ability to rapidly regulate synaptic transmission (Ryan, 1999; Lei et al., 2001). In addition, findings showing that MLCK is located in LA presynaptic terminals and in postsynaptic densities suggest that MLCK might be involved in regulating processes in these sites such as vesicle release (Ryan, 1999) or receptor activity (Lei et al., 2001). Moreover, the observation that MLCK inhibition does not affect fear memory retrieval implies that MLCK does not regulate transmission during memory activation, but only during acquisition. In addition, inhibition of myosin light chain kinase increased LTP in the auditory thalamic pathway to the LA (Lamprecht et al., 2006b). Application of ML-7 to amygdala slices had no effect on basal transmission but rather specifically on the induction of associative LTP. These findings show that the inhibition of MLCK facilitates conditioning and synaptic plasticity and indicate that MLCK normally inhibits fear learning.

3.4. MicroRNAs control of actin regulatory proteins in memory

MicroRNAs (miRNAs) are endogenous noncoding RNAs that are able to mediate cleavage or translational repression of their target mRNAs by direct binding to the 3′-UTR of target mRNAs (Filipowicz et al., 2008; Bartel, 2009). MiRNA targets include actin regulatory proteins. For example, the brain-specific microRNA, miR-134, is localized to the synapto-dendritic compartment of rat hippocampal neurons and negatively affects the size of spines by inhibition

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

of the translation of an mRNA encoding LIMK-1 (Schratt et al., 2006). Exposure of neurons to extracellular stimuli relieves miR-134 inhibition of LIMK-1 translation. Thus, the expression of miRNA can affect its target translation. Griggs et al. (2013) performed a microarray analysis in lateral amygdala 1 hr after fear conditioning. They revealed that miRNAs that can potentially repress the translation of actin-regulating proteins are down-regulated after training. Overexpression of one of these down-regulated miRNAs, miR-182, within the lateral amygdala resulted in decreased levels of the actin regulatory proteins cortactin and Rac1. The overexpression of miR-182 also impaired long-term but not short-term auditory fear memory. Thus, actin regulatory proteins are also being controlled at the protein level following learning. The effects of such changes may be related to later neuronal alterations needed for memory formation not immediately after learning.

Cumulatively, the aforementioned studies show that actin regulatory proteins are intimately involved in memory formation. Modulation of the actin cytoskeleton by these proteins may serve as a cellular signaling that connects synaptic activation initiated by learning to the cellular changes underlying memory formation. To further elucidate possible roles of actin cytoskeleton in memory formation the participation of actin cytoskeleton in synaptic morphology, transmission and plasticity in neurons is discussed below.

4. Actin cytoskeleton in synaptic transmission

Alteration of synaptic strength by affecting synaptic release of neurotransmitters and/or the level of synaptic receptors for neurotransmitters is associated with memory formation and synaptic plasticity. Changes in synaptic efficacy are induced by learning. For example, it was shown that fear-conditioning lead to presynaptic facilitation of AMPA receptor-mediated transmission in LA neurons (McKernan and Shinnick-Gallagher, 1997) and conditioned fear is accompanied by an enhancement of transmitter release at cortico-amygdala synapses (Tsvetkov et al., 2002). At the postsynapse fear conditioning drives AMPA receptors into LA synapses, a process that is needed for fear conditioning memory formation (Rumpel et al., 2005; Yeh et al., 2006; Nedelescu et al., 2010). Inhibitory avoidance (IA) drives AMPA receptors subunits into hippocampal synapse (Whitlock et al., 2006) and IA produces an enhancement of field excitatory postsynaptic potential (fEPSP) in hippocampus (Whitlock et al., 2006). Fear conditioning leads to recruitment of newly synthesized GluR1 selectively to mushroom-type spines in adult hippocampal CA1 neurons (Matsuo et al., 2008). Olfactory discrimination learning induces enhancement in the averaged amplitude of AMPA receptor-mediated miniature synaptic events in piriform cortex pyramidal neurons (Saar et al., 2012). GABA receptors are also involved in learning and memory for example, the averaged amplitude of GABA(A) receptor-mediated miniature inhibitory synaptic events was significantly enhanced following odor discrimination training (Saar et al., 2012).

Actin cytoskeleton located in pre- and post-synapse is involved in the regulation of synaptic transmission in these sites and may mediate changes in synaptic efficacy following learning. In the presynapse actin cytoskeleton contacts synaptic vesicle through short strands of synapsin, a phosphoprotein associated with synaptic vesicle membrane (e.g., Landis et al., 1988; Hirokawa et al., 1989; Doussau and Augustine, 2000). It is possible that actin regulates the availability of the vesicles in the reserve pool (RP) by forming a barrier (e.g., Wang et al., 1996) or may serve as a scaffold protein to retain synapsin in presynapse, thereby indirectly affecting neurotransmission (Sankaranarayanan et al., 2003). Neuronal activation may redistribute synapsin allowing access to the RP of vesicles (Greengard et al., 1994; Chi et al., 2001, 2003). Actin may also promote vesicle delivery to the readily releasable pool (RRP) by providing cytoskeletal routes of vesicle to the RRP (Prekeris and Terrian, 1997; Evans et al., 1998; Watanabe et al., 2005). In addition, actin may be involved in the endocytosis of vesicle at the presynapse, possibly by forming a link with dynamin or by promoting the transport of endocytosed vesicles to the internal RP cluster (Shupliakov et al., 2002; Bloom et al., 2003; Engqvist-Goldstein and Drubin, 2003). Synaptic vesicles endocytosed at one bouton can be recruited into the functional pool of nearby boutons where they undergo exocytosis (Darcy et al., 2006). Such distribution of vesicles between nearby boutons requires actin turnover (Darcy et al., 2006).

The postsynaptic actin cytoskeleton may affect synaptic transmission as it is involved in the regulation of glutamate and GABA receptors clustering and trafficking and by that means the postsynaptic response to neurotransmitters. F-actin depolymerization leads to a decrease in the number of AMPA and NMDA receptors clusters at excitatory synapses (Allison et al., 1998). Actin may also mediate glutamate receptors trafficking via myosins. Myosin Va mediates translocation of GluR1-containing AMPA receptor (AMPAR) from the dendritic shaft into spines and is needed for LTP (Correia et al., 2008). Myosin Vb is also involved in AMPAR trafficking (Lisé et al., 2006; Wang et al., 2008). Actin regulatory and associated proteins are also involved in receptor trafficking. For example, ADF/cofilin-mediated actin dynamics regulates AMPAR translocation during synaptic potentiation (Gu et al., 2010). The reversion induced LIM protein (RIL) is involved in actin-dependent trafficking of the AMPAR subunit GluR1 (Schulz et al., 2004) and the actin adaptor protein 4.1 N regulates the surface expression of GluR1 (Shen et al., 2000, Hayashi et al., 2005; Lin et al., 2009). The actin cytoskeleton also mediates AMPAR internalization. AMPAR internalization can be induced by the actin assembly inhibitor latrunculin A, and is blocked by jasplakinolide, a drug which stabilizes actin filaments (Zhou et al., 2001). Myosin VI plays a role in the clathrin-mediated endocytosis of AMPARs (Osterweil et al., 2005). Actin cytoskeleton can also affect inhibitory transmission by mediating GABA receptor trafficking to the synapse (e.g., Graziane et al., 2009).

Cumulatively, the aforementioned studies show that actin cytoskeleton is involved in regulating synaptic transmission by affecting pre- and post-synapse molecular and cellular events that are also involved in synaptic plasticity and memory formation. Additional research is warranted to determine whether actin cytoskeleton is needed for presynaptic or postsynaptic alterations during and following learning.

5. Actin cytoskeleton in synaptic morphogenesis

It has been shown that alteration in neuronal morphology is associated with memory formation (Bailey and Kandel, 1993; Lamprecht and LeDoux, 2004) and may be needed to modulate neuronal connectivity to form or alter memory. Most excitatory synapses in the brain terminate on spines, which have been the focus of recent studies pertaining to the mammalian brain. Spines receive the majority of excitatory synaptic inputs in the brain, compartmentalize local synaptic signaling pathways, and confine the diffusion of postsynaptic molecules (Nimchinsky et al., 2002; Lamprecht and LeDoux, 2004; Newpher and Ehlers, 2009). Modulation of the number of spines and/or their morphology has been proposed to contribute to changes in excitatory synaptic transmission following learning (Lamprecht and LeDoux, 2004). Changes in number and shape of spines were observed following learning. For example, an increase in spine number (density) was detected in the hippocampus 24 h after trace eyeblink conditioning, and these changes were blocked by NMDA antagonists (Leuner et al., 2003). An increase in the number of multiple

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

synaptic boutons that formed synapses on spines was also detected in the hippocampus 24 h after trace eyeblink conditioning (Geinisman et al., 2001). The number of synapses also increases in the cerebellum after eyeblink conditioning (Kleim et al., 2002) and in the piriform cortex following olfactory learning (Knafo et al., 2001). Repetitive motor learning leads to coordinated formation of clustered spines (Fu et al., 2012). In zebra finches, hearing a tutor song led to the rapid stabilization, accumulation and enlargement of spines in HVC (Roberts et al., 2010). In addition, contextual fear conditioning leads to a time-dependent increase in spine density in the CA1 hippocampal area and in the anterior cingulate cortex (Restivo et al., 2009; Vetere et al., 2011) and auditory fear conditioning leads to an increase in spinophilin-immunoreactive spines in the LA (Radley et al., 2006). Postsynaptic density (PSD) area on a smooth endoplasmic reticulum (sER)-free spines increases with fear conditioning whereas the spines head volume of these spines decreases (Ostroff et al., 2010).

Actin cytoskeleton is involved in neuronal morphogenesis in postsynaptic spines. The base, neck, and head of mature spine contain a mixture of branched and linear actin filaments. The neck includes both linear and branched filaments, whereas branched actin filament network is a dominant feature of spine head (Korobova and Svitkina, 2010). The actin cytoskeleton is intimately involved in the formation, elimination, stability, motility and morphology of spines (e.g., Halpain et al., 1998; Matus, 2000; Korkotian and Segal, 2001; Luo, 2002; Ethell and Pasquale, 2005; Tada and Sheng, 2006; Schubert and Dotti, 2007; Honkura et al., 2008; Hotulainen and Hoogenraad, 2010). In addition, actin plays a role in stabilizing postsynaptic proteins (Allison et al., 1998; Kuriu et al., 2006; Renner et al., 2009) and in modulating spine head structure following synaptic signaling (Fischer et al., 2000; Star et al., 2002; Okamoto et al., 2004). Ample studies have shown that actin regulatory proteins are also involved in regulating spine morphology (see above). For example, proteins that are involved in actin polymerization and depolymerization such as profilin (e.g. Ackermann and Matus, 2003) and cofillin (e.g. Rust et al., 2010) or proteins involved in actin branching such as Arp2/3 (e.g. Rácz and Weinberg, 2008; Wegner et al., 2008; Nakamura et al., 2011; Lippi et al., 2011) have been shown to regulate spine morphogenesis. Such proteins can couple intra- or extra-cellular signaling to neuronal morphogenesis by controlling actin dynamics and structure.

Alteration in axonal morphology is also implicated in synaptic plasticity and memory formation (Bailey and Kandel, 1993; Lamprecht and LeDoux, 2004). Actin polymerization mediates morphological changes involved in axonal growth, guidance, shape, collateral branching, branch retraction and regeneration (Luo, 2002; Letourneau, 2009).

Additional research is warranted to elucidate whether actin is involved in neuronal morphogenes is observed after learning and whether such changes are essential for memory formation. Some supporting evidence comes from studies showing that interference with actin regulatory proteins activity impairs memory formation and spine and axonal morphology (e.g. LIMK-1 (Meng et al., 2002); cofillin (e.g. Rust et al., 2010); ArpC3 (Kim et al., 2013); and see above).

6. The roles of actin cytoskeleton in synaptic plasticity

6.1. Synaptic plasticity and memory

As shown in the aforementioned studies actin cytoskeleton plays central roles in modulating synaptic transmission and neuronal morphogenesis, cellular processes believed to subserve synaptic plasticity (e.g. Bailey and Kandel, 1993; Lamprecht and LeDoux, 2004). The role of actin cytoskeleton in synaptic plasticity was studied mainly by elucidating its involvement in LTP or LTD, physiological models of memory (e.g., Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Martin et al., 2000). Findings relate LTP and LTD with learning and memory (e.g. Lynch, 2004, Collingridge et al., 2010). For example, inhibitors and genetic manipulation that impair hippocampal LTP also block hippocampal learning and memory retention. Intraventricular injection of the NMDA receptor antagonist AP-5 impaired hippocampal LTP and Morris water maze memory formation (Morris et al., 1986) and mice in which the deletion of the NMDAR1 gene was restricted to the hippocampal CA1 pyramidal cells were impaired in LTP in the CA1 synapses and in spatial memory (Tsien et al., 1996). One-trial inhibitory avoidance (IA) learning in rats produced similar changes in hippocampal AMPA glutamate receptors as induction of LTP with high frequency stimulation and caused a spatially restricted increase in the amplitude of evoked synaptic transmission in CA1 *in vivo*. On the basis of the observation that learning-induced synaptic potentiation occluded HFS-induced LTP, the authors conclude that IA training induces LTP in CA1 (Whitlock et al., 2006). Studies suggest that LTP occurs in the LA and hippocampus during fear conditioning. LTP induction at thalamic auditory inputs to the LA facilitates auditory-induced responses in the LA similarly to the increase of CS-evoked responses observed during auditory fear conditioning (Rogan and LeDoux, 1995). In addition, fear conditioning-altered auditory CS-evoked responses in LA changes together with conditioned fear responses (Rogan et al., 1997). Thalamic inputs or cortical inputs to the LA were enhanced in brain slices from trained animals compared to naive or unpaired animal groups (McKernan and Shinnick-Gallagher, 1997). Moreover, fear conditioning inhibits the induction of LTP at cortical inputs suggesting that LA synapses that have already undergone LTP by training are less capable of inducing LTP (Tsvetkov et al., 2002; Schroeder and Shinnick-Gallagher, 2004; and Schroeder and Shinnick-Gallagher, 2005). Studies have shown that contextual fear conditioning increased synaptic responses in hippocampal CA1 (e.g., Sacchetti et al., 2001) and that contextual fear conditioning altered the ability to induce LTP in hippocampus (Sacchetti et al., 2002). LTD is also implicated in learning and memory (e.g. Collingridge et al., 2010). For example, blocking the interactions between GluR2 and AP2 impaired LTD in perirhinal cortex *in vitro* and produced striking deficits in visual object recognition memory (Griffiths et al., 2008).

6.2. Actin in LTP

To study the roles of actin in LTP Okamoto et al. (2004) utilized the fluorescence resonance energy transfer (FRET) technique to show that LTP in rat hippocampal spines led to persistent shift of F-actin/G-actin equilibrium toward F-actin within seconds of a tetanic stimulus. In the dentate gyrus, LTP increased F-actin content in spines lasting up to 5 weeks (Fukazawa et al., 2003). The increase in F-actin correlated with increase in the size of the spine head and inhibition of actin polymerization impaired LTP-induced spine head enlargement (Matsuzaki et al., 2004; Okamoto et al., 2004; Fortin et al., 2010). LTP also induced alterations in axonal morphology and actin cytoskeleton leading to creation of new axonal varicosities and new axonal actin puncta (Colicos et al., 2001; De Paola et al., 2003). The new presynaptic actin puncta become associated with recycling synaptic vesicle pool (Colicos et al., 2001). Long-term facilitation leads to the growth of new synapses and presynaptic actin remodeling in Aplysia mechanosensory neurons (Hatada et al., 2000). In addition, cytochalasin D selectively impairs long-term but not short-term facilitation (Udo et al., 2005).

In LA, 5-HT-induced L-LTP is blocked by the actin inhibitor cytochalasin D (Huang and Kandel, 2007). Furthermore, LTP in interneurons in LA is maintained by trafficking of GluR2-lacking AMPA receptors that need an interaction with SAP97 and the actin

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

cytoskeleton (Polepalli et al., 2010). Inhibition of actin polymerization in hippocampus or disruption of F-actin cause an impairment of LTP formation and facilitation (e.g., Kim and Lisman, 1999; Krucker et al., 2000; Fukazawa et al., 2003; Kramár et al., 2009). In addition, inhibition of actin polymerization affects protein synthesis-independent early LTP, prevents late-LTP, and interferes with synaptic tagging in apical dendrites of hippocampal CA1 (Ramachandran and Frey, 2009). Furthermore, chemical forms of LTP in hippocampal cultures forms GluR1 and synaptophysin puncta and these cellular and molecular events require actin polymerization (Antonova et al., 2001). Taken together, the above observations indicate that the actin cytoskeleton is needed for LTP.

6.3. Actin in LTD

Actin cytoskeleton is also involved in LTD which in many instances induces opposite synaptic, morphological, and molecular events compared to LTP (e.g., Zhou et al., 2004; Asrar and Jia, 2013). LTD induces shifts the F-actin/G-actin equilibrium toward G-actin and decreases spine head volume with the disappearance of some spines (Okamoto et al., 2004). The actin stabilizing drug jasplakinolide, a compound that has also been reported to block AMPA receptor endocytosis (Zhou et al., 2001), was shown to prevent the long-lasting depression induced by (S)-3,5-Dihydroxyphenylglycine (DHPG), a specific group I metabotropic glutamate receptor (mGluR) agonist, in hippocampus neurons (Xiao et al., 2001). In another study the investigators infused the actin stabilizer phalloidin into hippocampal cells and observed that LTD was blocked (Morishita et al., 2005). Cofilin is also shown to be involved in regulating LTD (Zhou et al., 2004; Morishita et al., 2005). GluA2 regulates metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD) in N-cadherin-dependent and cofilin-mediated actin reorganization (Zhou et al., 2011). Furthermore, LTD-inducing paradigm has stabilizing effects on actin (Star et al., 2002).

6.4. Actin regulatory proteins in synaptic plasticity

6.4.1. Rho GTPases and synaptic plasticity

Synaptic plasticity is regulated by Rho GTPase family of proteins shown to be involved in memory formation. For example, in hippocampus the activation of RhoA and Rac1 by high frequency stimulation was attenuated by geranylgeranyl transferase inhibitor GGTI-287 and activation of RhoB was largely prevented by FTase inhibitor 1 (FTase inhibitor 1 can also reduce the levels of activated Ras). FTase inhibitor 1 reduced the magnitude of LTP while GGTI-287 markedly enhanced the magnitude of LTP. Inhibition of ROCK also increased the magnitude of LTP (O'Kane et al., 2004). In another study it was shown that early phase LTP is significantly reduced in RhoB−/− animals, whereas the later phase is unaffected (McNair et al., 2010). RhoB is also involved in the regulation of cofilin and dendritic and spine morphology (McNair et al., 2010). A general inhibitor of Rho GTPases, Clostridium difficile toxin B, significantly reduced the glutamate-induced potentiation of mEPSC frequency in hippocampal neurons (Wang et al., 2005). Inhibition of ROCK also reduced the potentiation of mEPSC frequency and amplitude. Inhibition of Rac1 GTPase in the hippocampus impaired the induction of NMDA receptor-dependent LTP, but did not have an effect on LTP maintenance and expression. The Rac1 GTPase inhibitor also impaired NMDA receptor-dependent induction of LTD, while mGluR-dependent LTD was shown to be altered but not eliminated (Martinez and Tejada-Simon, 2011). Adenosine infusion blocked theta burst stimulation (TBS)-induced actin polymerization within spines along with LTP itself in hippocampal slices but not in those slices pretreated with jasplakinolide that stabilizes actin filament (Rex et al., 2009). The authors further showed that the ROCK inhibitor reduced TBS-induced cofilin phosphorylation, spine actin polymerization and LTP. Inhibitors of Rac or PAK did prolong LTP's vulnerability to reversal by latrunculin. Ptprz-deficient mice that are impaired in memory formation (see above) exhibit enhancement of LTP in the CA1 region in hippocampal slices that is obliterated by pharmacological inhibition of ROCK (Niisato et al., 2005). Loss of Rac1 impaired LTP in both CA1 and dentate gyrus (Haditsch et al., 2009).

Cumulatively, the above observations suggest that stimuli that lead to induction of LTP activate synaptic receptors and modulate intracellular signaling proteins that regulate actin dynamics and structure. Interfering which such regulation impairs actin cytoskeleton responses to receptors activation and leads to impairments in synaptic plasticity.

6.4.2. Actin binding proteins and synaptic plasticity

Neuronal plasticity is also modulated by actin binding proteins. For example, the actin-capping protein, Eps8, is recruited to the spine head during LTP and inhibition of Eps8 capping activity impairs spine enlargement and potentiation (Menna et al., 2013). Another study shows that Eps8 induces the formation and maturation of spines and regulates actin dynamics and the balance between excitatory synapses on spines and the dendritic shaft (Stamatakou et al., 2013). This study also shows that Eps8 is needed for LTP-dependent structural plasticity of spines. Adducin, involved in actin capping, bundling, and in promoting spectrin binding to actin filaments (Gardner and Bennett, 1987; Mische et al., 1987; Kuhlman et al., 1996), is also needed for synaptic plasticity. β-adducin is needed for CA1 short- and long-term synaptic plasticity (Rabenstein et al., 2005). Mice lacking Tmod2, that encodes the actin capping protein Tropomodulin-2, have normal basal synaptic transmission at Schaffer collateral synapses as shown by input/output curves and the amplitude of the fiber volley (Cox et al., 2003). Paired-pulse facilitation (PPF) which indicates on presynaptic neurotransmitter release is normal in Tmod2 null mice. The study shows that there is an enhancement in LTP following PTP in mice lacking Tmod2 that could reflect an enhancement in induction or maintenance of LTP and suggesting that Tmod2 plays a role in synaptic plasticity.

Cumulatively, the aforementioned studies show that the actin cytoskeleton serves as regulator of synaptic plasticity possibly by affecting synaptic morphology and transmission and thereby tuning synaptic efficacy. Furthermore, the actin cytoskeleton is intimately involved in synaptic plasticity in brain regions involved in memory formation such as the amygdala and hippocampus.

7. Conclusions and discussion

Several additional conclusions and insights can be drawn from the above observations: (1) Although actin is involved in basic fundamental functions such as synaptic transmission and neuronal morphogenesis many studies show that interfering with actin cytoskeleton, or its regulatory proteins, functions has no effect on basal synaptic transmission but specifically on synaptic plasticity and memory formation. A tenable hypothesis is that actin cytoskeleton affects synaptic properties needed specifically for alterations in synaptic efficacy in a stimuli-dependent manner. These stimuli may be related to learning or stimuli leading to synaptic plasticity. (2) Table 1 shows that actin-regulatory proteins subserve the formation of different types of memory (e.g. spatial memory such as Morris water maze and aversive memory such as fear conditioning) in different organisms along the phyla. These observations suggest that different types of memory are mediated by similar cellular events subserved by the actin cytoskeleton. This is not unique to actin regulatory pathways as other pathways are found to subserve various behaviors and memories in different organisms (e.g. CREB-mediated transcription; Lamprecht, 1999).

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

Table 1
The roles of actin regulatory proteins in learning and memory.

Proteins	Effects on actin and cellular functions	Involvement in learning and memory	References
Rho GTPase family GAPs and GEFs	**Affect actin dynamics by regulating Rho GTPases**		
p190 RhoGAP	Affects actin reorganization; regulates axonal morphology.	Fear conditioning, Morris water maze.	Brouns et al., 2000; Billuart et al., 2001; Lamprecht et al., 2002; Niisato et al., 2005; Tamura et al., 2006
Oligophrenin1	Inhibits RhoA, Rac1, and Cdc42; colocalizes with actin; affects dendritic spine morphology.	Morris water maze.	Fauchereau et al., 2003; Govek et al., 2004; Khelfaoui et al., 2007.
Breakpoint cluster region (BCR) and active BCR-related (ABR)	RacGAP, affects dendritic spine density.	Morris water maze, object recognition memory.	Oh et al., 2010.
WRP	RacGAP, affects dendritic spine density.	Object recognition, water maze, passive avoidance memory.	Endris et al., 2002; Carlson et al., 2011.
KALRN	RacGEF, affects actin dynamics, glutamatergic transmission, spine density.	Morris water maze, Y-maze paradigm (KALRN), passive avoidance (kalirin7), fear conditioning.	Penzes et al., 2000, 2001; Ma et al., 2008 (Kalirin7); Cahill et al., 2009; Xie et al., 2011; Vanleeuwen and Penzes, 2012.
Rho GTPase family	**Affects actin dynamics via downstream signaling proteins**		
Rac GTPase	Affects actin dynamics by regulating molecules such as PAK, spine and synapse morphology.	**Inhibition/knockout** – slower decay of olfactory aversive conditioning memory (Drosophila), Impairs cocaine-induced place preference (CPP), Morris water maze, contextual fear extinction. **Activation** – enhancement of fear conditioning memory, Morris water maze, object recognition memory.	Diana et al., 2007; Sananbenesi et al., 2007; Corbetta et al., 2008; Haditsch et al., 2009; Shuai et al., 2010, 2011; De Viti et al., 2010; Borrelli et al., 2013; Ding et al., 2013
Rho GTPase family-regulated proteins	**Affecting actin by controlling actin-regulatory proteins**		
Rho-associated kinase	Affecting actin functions by regulating proteins such as myosin light chain phosphatase and LIM kinase (LIMK).	Fear conditioning, conditioned taste aversion, Morris water maze.	Lamprecht et al., 2002; Dash et al., 2004; Ota et al., 2010; Rozic et al., 2011; Sweetat et al., 2012
p21 activated kinase (PAK)	Inhibits cofilin activity via LIMK; affects dendritic spine number and morphology.	Morris water maze, contextual fear conditioning, active and passive avoidance, contextual fear conditioning memory extinction.	Hayashi et al., 2004; Sananbenesi et al., 2007; Nekrasova et al., 2008; Furnari et al., 2013
LIM-kinase (LIMK)	LIMK phosphorylates and inactivates the actin depolymerization factor cofilin; affects spine and axonal morphology.	LIMK-1 knockout mice show enhanced cued fear and impair reversal phase of Morris water maze.	Meng et al., 2002
Actin binding and regulatory proteins	**Proteins that directly control actin dynamics and structure**		
Cofilin	Severs and depolymerizes actin filaments; affects spine number and morphology.	Morris water maze learning, contextual and cued fear learning, conditioned place preference reward learning, object placement training, inhibitory avoidance, extinction of conditioned taste aversive.	Rust et al., 2010; Suzuki et al., 2011; Nelson et al., 2012; Wang et al., 2013
Arp2/3	Initiates branched filament polymerization to create actin meshworks; affects spine morphology.	Y maze, novel object recognition memory.	Kim et al., 2013
Filamin	F-actin cross linker protein.	Pavlovian olfactory LTM.	Bolduc et al., 2010
Eps8	Actin barbed end capping and actin bundling activities; affects neuronal morphology.	Radial maze, novel object recognition, passive avoidance.	Menna et al., 2013
Drebrin A	Stabilizing actin filaments.	Contextual fear conditioning memory.	Kojima et al., 2010
Adducin	Caps and bundles barbed end of actin filaments and promotes spectrin binding to actin filaments; affects spine morphology.	Morris water maze, cued and contextual fear conditioning memory, environmental-enhanced long-term memory of contextual fear conditioning and novel object recognition, olfactory associative memory.	Rabenstein et al., 2005; Porro et al., 2010; Bednarek and Caroni, 2011; Ruediger et al., 2011; Vukojevic et al., 2012
Tropomodulin	Pointed-end actin capping protein.	Contextual and cued conditioned fear, Morris water maze.	Cox et al., 2003
Neubrin/spinophilin	Actin binding protein.	Contextual fear memory, conditioned taste aversion (CTA).	Stafstrom-Davis et al., 2001; Wu et al., 2008
Profilin	Funnels ATP-actin monomers to the growing actin filaments; affects spine morphology.	Fear conditioning in rats induces the translocation of profilin into dendritic spine in the LA.	Lamprecht et al., 2006a
Myosin II and myosin light chain kinase (MLCK)	Actin binding motor protein and regulator.	Cued and contextual fear conditioning.	Lamprecht et al., 2006b; Rex et al., 2010; Gavin et al., 2011

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

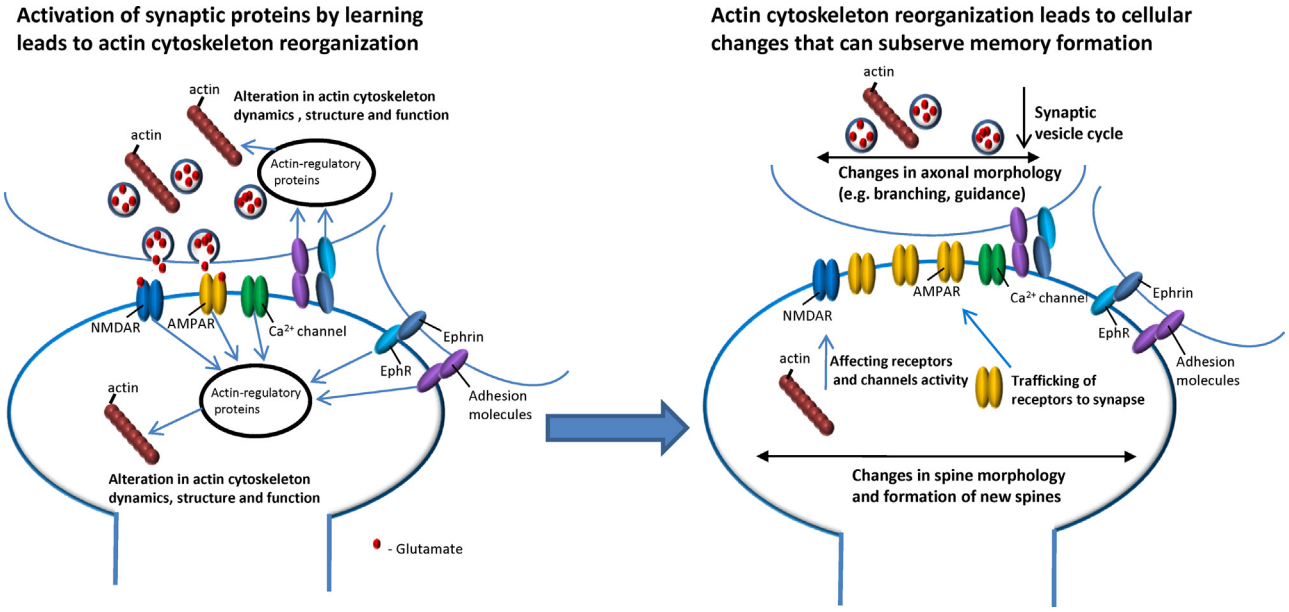

Fig. 2. A model for cellular changes subserved by the actin cytoskeleton that may lead to alteration in synaptic efficacy and memory formation. Learning leads to activation of synaptic receptors and channels that leads to changes in actin cytoskeleton dynamics and structure by actin-regulatory proteins. Such alterations in actin were shown to subserve changes in neuronal morphology and in synaptic transmission. These cellular events are believed to underlie memory formation.

(3) The actin cytoskeleton and its regulatory proteins are involved in various stages of memory. They are involved in memory consolidation, reconsolidation and extinction. These findings suggest that similar cellular events mediated by the actin cytoskeleton are involved in these memory stages. For example, memory consolidation and extinction involve spine morphogenesis. (4) Interruption of actin cytoskeleton mediated functions is sufficient for disruption of memory formation. Other cellular functions shown to be essential for memory formation such as protein synthesis could be mediated by actin cytoskeleton or are needed for memory formation in addition to actin cytoskeleton (at same or different time points). (5) Studies have shown that proteins involved in processes leading to opposite outcomes at the molecular level (e.g. inhibiting or activating Rho GTPase or Rac GTPase) lead to similar behavioral outcome such as memory impairment. It might be that the various pathways affecting actin are activated in different temporal and spatial manner and the participating proteins are engaged at different time points during memory formation and at different micro-regions of the neurons. The studies described in the review showing the effects of these proteins on memory formation utilize techniques that affect actin and its regulatory protein in a relatively low temporal and spatial resolution. Thus, current techniques described in studies do not allow dissecting the functions of these proteins at high resolution *in vivo*.

8. Actin cytoskeleton – a mediator between synaptic signaling during learning and cellular events involved in memory formation and extinction

Based on the studies above the following sequence of events leading to memory formation that involve the actin cytoskeleton is suggested (Fig.. 2). Learning induces a significant activation of synaptic receptors and channels above a certain threshold (for fear conditioning see Blair et al., 2001) leading to the activation of intracellular signaling pathways and to alteration of actin cytoskeleton dynamics, actin filaments structure and interaction. These changes in actin filament may support multiple key cellular events that include modulation of neurotransmitter receptors at the synapse and alteration in synapse and spine morphology. Such changes have shown to alter synaptic efficacy and believed to be essential for alteration in connectivity between neurons which constitute the changes in neuronal circuits leading to memory storage.

9. Future research

Much evidence indicates that the actin cytoskeleton and its regulatory proteins are involved in memory formation. However, key questions remain unanswered. For example, are the morphological changes shown to be mediated by actin cytoskeleton, such as shown in spines and axons, needed for memory formation? Does actin cytoskeleton regulate changes in synaptic transmission needed for memory formation? If so, are they related to presynaptic (changes in vesicle release) or postsynaptic (changes in receptor trafficking) alterations or to both? Studies aimed to clarify such questions at high spatiotemporal resolution will undoubtedly provide key insights into the roles of actin cytoskeleton in memory and will afford insight into cellular events underpinning memory formation and greatly contribute to a better elucidation of the intricate molecular and cellular processes governing memory formation.

References

Abou-Kheir, W., Isaac, B., Yamaguchi, H., Cox, D., 2008. Membrane targeting of WAVE2 is not sufficient for WAVE2-dependent actin polymerization: a role for IRSp53 in mediating the interaction between Rac and WAVE2. J. Cell Sci. 121, 379–390.

Ackermann, M., Matus, A., 2003. Activity-induced targeting of profilin and stabilization of dendritic spine morphology. Nat. Neurosci. 6, 1194–1200.

Akasu, T., Ito, M., Nakano, T., Schneider, C.R., Simmons, M.A., Tanaka, T., Tokimasa, T., Yoshida, M., 1993. Myosin light chain kinase occurs in bullfrog sympathetic neurons and may modulate voltage-dependent potassium currents. Neuron 11, 1133–1145.

Allen, P.B., Ouimet, C.C., Greengard, P., 1997. Spinophilin, a novel protein phosphatase 1 binding protein localized to dendritic spines. Proc. Natl. Acad. Sci. U.S.A. 94, 9956–9961.

Allingham, J.S., Smith, R., Rayment, I., 2005. The structural basis of blebbistatin inhibition and specificity for myosin II. Nat. Struct. Mol. Biol. 12, 378–379.

Allison, D.W., Gelfand, V.I., Spector, I., Craig, A.M., 1998. Role of actin in anchoring postsynaptic receptors in cultured hippocampal neurons: differential attachment of NMDA versus AMPA receptors. J. Neurosci. 18, 2423–2436.

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

Amano, M., Nakayama, M., Kaibuchi, K., 2010. Rho-kinase/ROCK: A key regulator of the cytoskeleton and cell polarity. Cytoskeleton 67, 545–554.
Antonova, I., Arancio, O., Trillat, A.C., Wang, H.G., Zablow, L., Udo, H., Kandel, E.R., Hawkins, R.D., 2001. Rapid increase in clusters of presynaptic proteins at onset of long-lasting potentiation. Science 294, 1547–1550.
Aoki, C., Sekino, Y., Hanamura, K., Fujisawa, S., Mahadomrongkul, V., Ren, Y., Shirao, T., 2005. Drebrin A is a postsynaptic protein that localizes in vivo to the submembranous surface of dendritic sites forming excitatory synapses. J. Comp. Neurol. 483, 383–402.
Arber, S., Barbayannis, F.A., Hanser, H., Schneider, C., Stanyon, C.A., Bernard, O., Caroni, P., 1998. Regulation of actin dynamics through phosphorylation of cofilin by LIM-kinase. Nature 393, 805–809.
Asrar, S., Jia, Z., 2013. Molecular mechanisms coordinating functional and morphological plasticity at the synapse: role of GluA2/N-cadherin interaction-mediated actin signaling in mGluR-dependent LTD. Cell Signal. 25, 397–402.
Bailey, C.H., Kandel, E.R., 1993. Structural changes accompanying memory storage. Annu. Rev. Physiol. 55, 397–426.
Bamburg, J.R., Bernstein, B.W., 2008. ADF/cofilin. Curr. Biol. 18, R273–R275.
Bartel, D.P., 2009. MicroRNAs: target recognition and regulatory functions. Cell 136, 215–233.
Bear, J.E., Rawls, J.F., Saxe III, C.L., 1998. SCAR, a WASP-related protein, isolated as a suppressor of receptor defects in late Dictyostelium development. J. Cell Biol. 142, 1325–1335.
Bednarek, E., Caroni, P., 2011. β-Adducin is required for stable assembly of new synapses and improved memory upon environmental enrichment. Neuron 69, 1132–1146.
Bi, A.L., Wang, Y., Li, B.Q., Wang, Q.Q., Ma, L., Yu, H., Zhao, L., Chen, Z.Y., 2010. Region-specific involvement of actin rearrangement-related synaptic structure alterations in conditioned taste aversion memory. Learn. Mem. 17, 420–427.
Billuart, P., Winter, C.G., Maresh, A., Zhao, X., Luo, L., 2001. Regulating axon branch stability: the role of p190 RhoGAP in repressing a retraction signaling pathway. Cell 107, 195–207.
Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M., LeDoux, J.E., 2001. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn. Mem. 8, 229–242.
Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361, 31–39.
Bloom, O., Evergren, E., Tomilin, N., Kjaerulff, O., Löw, P., Brodin, L., Pieribone, V.A., Greengard, P., Shupliakov, O., 2003. Colocalization of synapsin and actin during synaptic vesicle recycling. J. Cell Biol. 161, 737–747.
Bokoch, G.M., 2003. Biology of the p21-activated kinases. Annu. Rev. Biochem. 72, 743–781.
Bolduc, F.V., Bell, K., Rosenfelt, C., Cox, H., Tully, T., 2010. Fragile x mental retardation 1 and filamin a interact genetically in Drosophila long-term memory. Front. Neural Circuits 3, 22.
Borrelli, S., Musilli, M., Martino, A., Diana, G., 2013. Long-lasting efficacy of the cognitive enhancer cytotoxic necrotizing factor 1. Neuropharmacology 64, 74–80.
Bouton, M.E., 1994. Conditioning, remembering, and forgetting. J. Exp. Psychol. Anim. Behav. Process. 20, 219–231.
Brouns, M.R., Matheson, S.F., Hu, K.Q., Delalle, I., Caviness, V.S., Silver, J., Bronson, R.T., Settleman, J., 2000. The adhesion signaling molecule p190 RhoGAP is required for morphogenetic processes in neural development. Development 127, 4891–4903.
Brouns, M.R., Matheson, S.F., Settleman, J., 2001. p190 RhoGAP is the principal Src substrate in brain and regulates axon outgrowth, guidance and fasciculation. Nat. Cell Biol. 3, 361–367.
Brusés, J.L., 2006. N-Cadherin signaling in synapse formation and neuronal physiology. Mol. Neurobiol. 33, 237–252.
Cahill, M.E., Xie, Z., Day, M., Photowala, H., Barbolina, M.V., Miller, C.A., Weiss, C., Radulovic, J., Sweatt, J.D., Disterhoft, J.F., Surmeier, D.J., Penzes, P., 2009. Kalirin regulates cortical spine morphogenesis and disease-related behavioral phenotypes. Proc. Natl. Acad. Sci. U.S.A. 106, 13058–13063.
Carlson, B.R., Lloyd, K.E., Kruszewski, A., Kim, I.H., Rodriguiz, R.M., Heindel, C., Faytell, M., Dudek, S.M., Wetsel, W.C., Soderling, S.H., 2011. WRP/srGAP3 facilitates the initiation of spine development by an inverse F-BAR domain, and its loss impairs long-term memory. J. Neurosci. 31, 2447–2460.
Cheng, D., Hoogenraad, C.C., Rush, J., Ramm, E., Schlager, M.A., Duong, D.M., Xu, P., Wijayawardana, S.R., Hanfelt, J., Nakagawa, T., Sheng, M., Peng, J., 2006. Relative and absolute quantification of postsynaptic density proteome isolated from rat forebrain and cerebellum. Mol. Cell Proteomics 5, 1158–1170.
Chi, P., Greengard, P., Ryan, T.A., 2001. Synapsin dispersion and reclustering during synaptic activity. Nat. Neurosci. 4, 1187–1193.
Chi, P., Greengard, P., Ryan, T.A., 2003. Synaptic vesicle mobilization is regulated by distinct synapsin I phosphorylation pathways at different frequencies. Neuron 38, 69–78.
Cho, Y.J., Cunnick, J.M., Yi, S.J., Kaartinen, V., Groffen, J., Heisterkamp, N., 2007. Abr and Bcr, two homologous Rac GTPase-activating proteins, control multiple cellular functions of murine macrophages. Mol. Cell Biol. 27, 899–911.
Chuang, T.H., Xu, X., Kaartinen, V., Heisterkamp, N., Groffen, J., Bokoch, G.M., 1995. Abr and Bcr are multifunctional regulators of the Rho GTP-binding protein family. Proc. Natl. Acad. Sci. U.S.A. 92, 10282–10286.
Cingolani, L.A., Goda, Y., 2008. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat. Rev. Neurosci. 9, 344–356.
Colicos, M.A., Collins, B.E., Sailor, M.J., Goda, Y., 2001. Remodeling of synaptic actin induced by photoconductive stimulation. Cell 107, 605–616.
Collingridge, G.L., Peineau, S., Howland, J.G., Wang, Y.T., 2010. Long-term depression in the CNS. Nat. Rev. Neurosci. 11, 459–473.
Corbetta, S., D'Adamo, P., Gualdoni, S., Braschi, C., Berardi, N., de Curtis, I., 2008. Hyperactivity and novelty-induced hyperreactivity in mice lacking Rac3. Behav. Brain Res. 186, 246–255.
Correia, S.S., Bassani, S., Brown, T.C., Lisé, M.F., Backos, D.S., El-Husseini, A., Passafaro, M., Esteban, J.A., 2008. Motor protein-dependent transport of AMPA receptors into spines during long-term potentiation. Nat. Neurosci. 11, 457–466.
Cox, P.R., Fowler, V., Xu, B., Sweatt, J.D., Paylor, R., Zoghbi, H.Y., 2003. Mice lacking Tropomodulin-2 show enhanced long-term potentiation, hyperactivity, and deficits in learning and memory. Mol. Cell Neurosci. 23, 1–12.
Darcy, K.J., Staras, K., Collinson, L.M., Goda, Y., 2006. Constitutive sharing of recycling synaptic vesicles between presynaptic boutons. Nat. Neurosci. 9, 315–321.
Dash, P.K., Orsi, S.A., Moody, M., Moore, A.N., 2004. A role for hippocampal Rho-ROCK pathway in long-term spatial memory. Biochem. Biophys. Res. Commun. 322, 893–898.
De Paola, V., Arber, S., Caroni, P., 2003. AMPA receptors regulate dynamic equilibrium of presynaptic terminals in mature hippocampal networks. Nat. Neurosci. 6, 491–500.
De Viti, S., Martino, A., Musilli, M., Fiorentini, C., Diana, G., 2010. The Rho GTPase activating CNF1 improves associative working memory for object-in-place. Behav. Brain Res. 212, 78–83.
Diana, G., Valentini, G., Travaglione, S., Falzano, L., Pieri, M., Zona, C., Meschini, S., Fabbri, A., Fiorentini, C., 2007. Enhancement of learning and memory after activation of cerebral Rho GTPases. Proc. Natl. Acad. Sci. U.S.A. 104, 636–641.
Diekmann, D., Brill, S., Garrett, M.D., Totty, N., Hsuan, J., Monfries, C., Hall, C., Lim, L., Hall, A., 1991. Bcr encodes a GTPase-activating protein for p21rac. Nature 351, 400–402.
Dillon, C., Goda, Y., 2005. The actin cytoskeleton: integrating form and function at the synapse. Annu. Rev. Neurosci. 28, 25–55.
Ding, Z.B., Wu, P., Luo, Y.X., Shi, H.S., Shen, H.W., Wang, S.J., Lu, L., 2013. Region-specific role of Rac in nucleus accumbens core and basolateral amygdala in consolidation and reconsolidation of cocaine-associated cue memory in rats. Psychopharmacology 228, 427–437.
Disanza, A., Carlier, M.F., Stradal, T.E., Didry, D., Frittoli, E., Confalonieri, S., Croce, A., Wehland, J., Di Fiore, P.P., Scita, G., 2004. Eps8 controls actin-based motility by capping the barbed ends of actin filaments. Nat. Cell Biol. 6, 1180–1188.
Disanza, A., Mantoani, S., Hertzog, M., Gerboth, S., Frittoli, E., Steffen, A., Berhoerster, K., Kreienkamp, H.J., Milanesi, F., Di Fiore, P.P., Ciliberto, A., Stradal, T.E., Scita, G., 2006. Regulation of cell shape by Cdc42 is mediated by the synergic actin-bundling activity of the Eps8-IRSp53 complex. Nat. Cell Biol. 8, 1337–1347.
Dong, L., Chapline, C., Mousseau, B., Fowler, L., Ramsay, K., Stevens, J.L., Jaken, S., 1995. 35H, a sequence isolated as a protein kinase C binding protein, is a novel member of the adducin family. J. Biol. Chem. 270, 25534–25540.
Doussau, F., Augustine, G.J., 2000. The actin cytoskeleton and neurotransmitter release: an overview. Biochimie 82, 353–363.
Dudai, Y., 1989. The Neurobiology of Memory. Oxford University Press, New York.
Eden, S., Rohatgi, R., Podtelejnikov, A.V., Mann, M., Kirschner, M.W., 2002. Mechanism of regulation of WAVE1-induced actin nucleation by Rac1 and Nck. Nature 418, 790–793.
Edwards, D.C., Sanders, L.C., Bokoch, G.M., Gill, G.N., 1999. Activation of LIM-kinase by Pak1 couples Rac/Cdc42 GTPase signalling to actin cytoskeletal dynamics. Nat. Cell Biol. 1, 253–259.
Egea, J., Klein, R., 2007. Bidirectional Eph-ephrin signaling during axon guidance. Trends Cell Biol. 17, 230–238.
Endris, V., Wogatzky, B., Leimer, U., Bartsch, D., Zatyka, M., Latif, F., Maher, E.R., Tariverdian, G., Kirsch, S., Karch, D., Rappold, G.A., 2002. The novel Rho-GTPase activating gene MEGAP/srGAP3 has a putative role in severe mental retardation. Proc. Natl. Acad. Sci. U.S.A. 99, 11754–11759.
Engqvist-Goldstein, A.E., Drubin, D.G., 2003. Actin assembly and endocytosis: from yeast to mammals. Annu. Rev. Cell Dev. Biol. 19, 287–332.
Ethell, I.M., Pasquale, E.B., 2005. Molecular mechanisms of dendritic spine development and remodeling. Prog. Neurobiol. 75, 161–205.
Evans, L.L., Lee, A.J., Bridgman, P.C., Mooseker, M.S., 1998. Vesicle-associated brain myosin-V can be activated to catalyze actin-based transport. J. Cell Sci. 111, 2055–2066.
Fauchereau, F., Herbrand, U., Chafey, P., Eberth, A., Koulakoff, A., Vinet, M.C., Ahmadian, M.R., Chelly, J., Billuart, P., 2003. The RhoGAP activity of OPHN1, a new F-actin-binding protein, is negatively controlled by its amino-terminal domain. Mol. Cell. Neurosci. 23, 574–586.
Fedulov, V., Rex, C.S., Simmons, D.A., Palmer, L., Gall, C.M., Lynch, G., 2007. Evidence that long-term potentiation occurs within individual hippocampal synapses during learning. J. Neurosci. 27, 8031–8039.
Filipowicz, W., Bhattacharyya, S.N., Sonenberg, N., 2008. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat. Rev. Genet. 9, 102–114.
Fischer, M., Kaech, S., Wagner, U., Brinkhaus, H., Matus, A., 2000. Glutamate receptors regulate actin-based plasticity in dendritic spines. Nat. Neurosci. 3, 887–894.
Fischer, A., Sananbenesi, F., Schrick, C., Spiess, J., Radulovic, J., 2004. Distinct roles of hippocampal de novo protein synthesis and actin rearrangement in extinction of contextual fear. J. Neurosci. 24, 1962–1966.
Fortin, D.A., Davare, M.A., Srivastava, T., Brady, J.D., Nygaard, S., Derkach, V.A., Soderling, T.R., 2010. Long-term potentiation-dependent spine enlargement

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

requires synaptic Ca^{2+}-permeable AMPA receptors recruited by CaM-kinase I. J. Neurosci. 30, 11565–11575.
Fu, M., Yu, X., Lu, J., Zuo, Y., 2012. Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. Nature 483, 92–95.
Fukazawa, Y., Saitoh, Y., Ozawa, F., Ohta, Y., Mizuno, K., Inokuchi, K., 2003. Hippocampal LTP is accompanied by enhanced F-actin content within the dendritic spine that is essential for late LTP maintenance in vivo. Neuron 38, 447–460.
Furnari, M.A., Jobes, M.L., Nekrasova, T., Minden, A., Wagner, G.C., 2013. Functional deficits in PAK5, PAK6 and PAK5/PAK6 knockout mice. PLoS ONE 8, e61321.
Gallo, G., Yee Jr., H.F., Letourneau, P.C., 2002. Actin turnover is required to prevent axon retraction driven by endogenous actomyosin contractility. J. Cell Biol. 158, 1219–1228.
Ganeshina, O., Erdmann, J., Tiberi, S., Vorobyev, M., Menzel, R., 2012. Depolymerization of actin facilitates memory formation in an insect. Biol. Lett. 8, 1023–1027.
Gardner, K., Bennett, V., 1987. Modulation of spectrin-actin assembly by erythrocyte adducin. Nature 328, 359–362.
Gavin, C.F., Rubio, M.D., Young, E., Miller, C., Rumbaugh, G., 2011. Myosin II motor activity in the lateral amygdala is required for fear memory consolidation. Learn. Mem. 19, 9–14.
Geinisman, Y., Berry, R.W., Disterhoft, J.F., Power, J.M., Van der Zee, E.A., 2001. Associative learning elicits the formation of multiple-synapse boutons. J. Neurosci. 21, 5568–5573.
Gerlai, R., Shinsky, N., Shih, A., Williams, P., Winer, J., Armanini, M., Cairns, B., Winslow, J., Gao, W., Phillips, H.S., 1999. Regulation of learning by EphA receptors: a protein targeting study. J. Neurosci. 19, 9538–9549.
Govek, E.E., Newey, S.E., Akerman, C.J., Cross, J.R., Van der Veken, L., Van Aelst, L., 2004. The X-linked mental retardation protein oligophrenin-1 is required for dendritic spine morphogenesis. Nat. Neurosci. 7, 364–372.
Govind, S., Kozma, R., Monfries, C., Lim, L., Ahmed, S., 2001. Cdc42Hs facilitates cytoskeletal reorganization and neurite outgrowth by localizing the 58-kD insulin receptor substrate to filamentous actin. J. Cell Biol. 152, 579–594.
Graziane, N.M., Yuen, E.Y., Yan, Z., 2009. Dopamine D4 receptors regulate GABAA receptor trafficking via an actin/cofilin/myosin-dependent mechanism. J. Biol. Chem. 284, 8329–8336.
Greengard, P., Benfenati, F., Valtorta, F., 1994. Synapsin I, an actin-binding protein regulating synaptic vesicle traffic in the nerve terminal. Adv. Second Messenger Phosphoprotein Res. 29, 31–45.
Griffiths, S., Scott, H., Glover, C., Bienemann, A., Ghorbel, M.T., Uney, J., Brown, M.W., Warburton, E.C., Bashir, Z.I., 2008. Expression of long-term depression underlies visual recognition memory. Neuron 58, 186–194.
Griggs, E.M., Young, E.J., Rumbaugh, G., Miller, C.A., 2013. MicroRNA-182 regulates amygdala-dependent memory formation. J. Neurosci. 33, 1734–1740.
Gu, J., Lee, C.W., Fan, Y., Komlos, D., Tang, X., Sun, C., Yu, K., Hartzell, H.C., Chen, G., Bamburg, J.R., Zheng, J.Q., 2010. ADF/cofilin-mediated actin dynamics regulate AMPA receptor trafficking during synaptic plasticity. Nat. Neurosci. 13, 1208–1215.
Haditsch, U., Leone, D.P., Farinelli, M., Chrostek-Grashoff, A., Brakebusch, C., Mansuy, I.M., McConnell, S.K., Palmer, T.D., 2009. A central role for the small GTPase Rac1 in hippocampal plasticity and spatial learning and memory. Mol. Cell. Neurosci. 41, 409–419.
Hall, A., Lalli, G., 2010. Rho and Ras GTPases in axon growth, guidance, and branching. Cold Spring Harb. Perspect. Biol. 2, a001818.
Halpain, S., Hipolito, A., Saffer, L., 1998. Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. J. Neurosci. 18, 9835–9844.
Hatada, Y., Wu, F., Sun, Z.Y., Schacher, S., Goldberg, D.J., 2000. Presynaptic morphological changes associated with long-term synaptic facilitation are triggered by actin polymerization at preexisting varicositis. J. Neurosci. 20, RC82.
Hayashi, K., Ishikawa, R., Ye, L.H., He, X.L., Takata, K., Kohama, K., Shirao, T., 1996. Modulatory role of drebrin on the cytoskeleton within dendritic spines in the rat cerebral cortex. J. Neurosci. 16, 7161–7170.
Hayashi, M.L., Choi, S.Y., Rao, B.S., Jung, H.Y., Lee, H.K., Zhang, D., Chattarji, S., Kirkwood, A., Tonegawa, S., 2004. Altered cortical synaptic morphology and impaired memory consolidation in forebrain-specific dominant-negative PAK transgenic mice. Neuron 42, 773–787.
Hayashi, T., Rumbaugh, G., Huganir, R.L., 2005. Differential regulation of AMPA receptor subunit trafficking by palmitoylation of two distinct sites. Neuron 47, 709–723.
Heasman, S.J., Ridley, A.J., 2008. Mammalian Rho GTPases: new insights into their functions from in vivo studies. Nat. Rev. Mol. Cell Biol. 9, 690–701.
Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. Wiley, New York.
Heisterkamp, N., Kaartinen, V., van Soest, S., Bokoch, G.M., Groffen, J., 1993. Human ABR encodes a protein with GAPrac activity and homology to the DBL nucleotide exchange factor domain. J. Biol. Chem. 268, 16903–16906.
Hirokawa, N., Sobue, K., Kanda, K., Harada, A., Yorifuji, H., 1989. The cytoskeletal architecture of the presynaptic terminal and molecular structure of synapsin 1. J. Cell Biol. 108, 111–126.
Honkura, N., Matsuzaki, M., Noguchi, J., Ellis-Davies, G.C., Kasai, H., 2008. The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines. Neuron 57, 719–729.
Hori, K., Yasuda, H., Konno, D., Maruoka, H., Tsumoto, T., Sobue, K., 2005. NMDA receptor-dependent synaptic translocation of insulin receptor substrate p53 via protein kinase C signaling. J. Neurosci. 25, 2670–2681.
Hotulainen, P., Hoogenraad, C.C., 2010. Actin in dendritic spines: connecting dynamics to function. J. Cell Biol. 189, 619–629.
Hou, Y.Y., Lu, B., Li, M., Liu, Y., Chen, J., Chi, Z.Q., Liu, J.G., 2009. Involvement of actin rearrangements within the amygdala and the dorsal hippocampus in aversive memories of drug withdrawal in acute morphine-dependent rats. J. Neurosci. 29, 12244–12254.
Huang, Y.Y., Kandel, E.R., 2007. 5-Hydroxytryptamine induces a protein kinase A/mitogen-activated protein kinase-mediated and macromolecular synthesis-dependent late phase of long-term potentiation in the amygdala. J. Neurosci. 27, 3111–3119.
Huang, W., Zhu, P.J., Zhang, S., Zhou, H., Stoica, L., Galiano, M., Krnjević, K., Roman, G., Costa-Mattioli, M., 2013. mTORC2 controls actin polymerization required for consolidation of long-term memory. Nat. Neurosci. 16, 441–448.
Hughes, C.A., Bennett, V., 1995. Adducin: a physical model with implications for function in assembly of spectrin-actin complexes. J. Biol. Chem. 270, 18990–18996.
Irie, F., Yamaguchi, Y., 2002. EphB receptors regulate dendritic spine development via intersectin, Cdc42 and N-WASP. Nat. Neurosci. 5, 1117–1118.
Kaartinen, V., Gonzalez-Gomez, I., Voncken, J.W., Haataja, L., Faure, E., Nagy, A., Groffen, J., Heisterkamp, N., 2001. Abnormal function of astroglia lacking Abr and Bcr RacGAPs. Development 128, 4217–4227.
Kamm, K.E., Stull, J.T., 2001. Dedicated myosin light chain kinases with diverse cellular functions. J. Biol. Chem. 276, 4527–4530.
Kandel, E.R., 2001. The molecular biology of memory storage: a dialogue between genes and synapses. Science 294, 1030–1038.
Khelfaoui, M., Denis, C., van Galen, E., de Bock, F., Schmitt, A., Houbron, C., Morice, E., Giros, B., Ramakers, G., Fagni, L., Chelly, J., Nosten-Bertrand, M., Billuart, P., 2007. Loss of X-linked mental retardation gene oligophrenin1 in mice impairs spatial memory and leads to ventricular enlargement and dendritic spine immaturity. J. Neurosci. 27, 9439–9450.
Kim, C.H., Lisman, J.E., 1999. A role of actin filament in synaptic transmission and long-term potentiation. J. Neurosci. 19, 4314–4324.
Kim, I.H., Park, S.K., Hong, S.T., Jo, Y.S., Kim, E.J., Park, E.H., Han, S.B., Shin, H.S., Sun, W., Kim, H.T., Soderling, S.H., Kim, H., 2009a. Inositol 1,4,5-trisphosphate 3-kinase a functions as a scaffold for synaptic Rac signaling. J. Neurosci. 29, 14039–14049.
Kim, I.H., Racz, B., Wang, H., Burianek, L., Weinberg, R., Yasuda, R., Wetsel, W.C., Soderling, S.H., 2013. Disruption of Arp2/3 results in asymmetric structural plasticity of dendritic spines and progressive synaptic and behavioral abnormalities. J. Neurosci. 33, 6081–6092.
Kim, M.H., Choi, J., Yang, J., Chung, W., Kim, J.H., Paik, S.K., Kim, K., Han, S., Won, H., Bae, Y.S., Cho, S.H., Seo, J., Bae, Y.C., Choi, S.Y., Kim, E., 2009b. Enhanced NMDA receptor-mediated synaptic transmission, enhanced long-term potentiation, and impaired learning and memory in mice lacking IRSp53. J. Neurosci. 29, 1586–1595.
Kleim, J.A., Freeman Jr., J.H., Bruneau, R., Nolan, B.C., Cooper, N.R., Zook, A., Walters, D., 2002. Synapse formation is associated with memory storage in the cerebellum. Proc. Natl. Acad. Sci. U.S.A. 99, 13228–13231.
Klein, R., 2009. Bidirectional modulation of synaptic functions by Eph/ephrin signaling. Nat. Neurosci. 12, 15–20.
Knafo, S., Grossman, Y., Barkai, E., Benshalom, G., 2001. Olfactory learning is associated with increased spine density along apical dendrites of pyramidal neurons in the rat piriform cortex. Eur. J. Neurosci. 13, 633–638.
Kneussel, M., Wagner, W., 2013. Myosin motors at neuronal synapses: drivers of membrane transport and actin dynamics. Nat. Rev. Neurosci. 14, 233–247.
Kojima, N., Hanamura, K., Yamazaki, H., Ikeda, T., Itohara, S., Shirao, T., 2010. Genetic disruption of the alternative splicing of drebrin gene impairs context-dependent fear learning in adulthood. Neuroscience 165, 138–150.
Konorski, J., 1948. Conditioned Reflexes and Neuron Organization. Cambridge University Press, Cambridge.
Korkotian, E., Segal, M., 2001. Regulation of dendritic spine motility in cultured hippocampal neurons. J. Neurosci. 21, 6115–6124.
Korobova, F., Svitkina, T., 2010. Molecular architecture of synaptic actin cytoskeleton in hippocampal neurons reveals a mechanism of dendritic spine morphogenesis. Mol. Biol. Cell 21, 165–176.
Kovacs, M., Toth, J., Hetenyi, C., Malnasi-Csizmadia, A., Sellers, J.R., 2004. Mechanism of blebbistatin inhibition of Myosin II. J. Biol. Chem. 279, 35557–35563.
Kramár, E.A., Chen, L.Y., Brandon, N.J., Rex, C.S., Liu, F., Gall, C.M., Lynch, G., 2009. Cytoskeletal changes underlie estrogen's acute effects on synaptic transmission and plasticity. J. Neurosci. 29, 12982–12993.
Krucker, T., Siggins, G.R., Halpain, S., 2000. Dynamic actin filaments are required for stable long-term potentiation (LTP) in area CA1 of the hippocampus. Proc. Natl. Acad. Sci. U.S.A. 97, 6856–6861.
Krugmann, S., Jordens, I., Gevaert, K., Driessens, M., Vandekerckhove, J., Hall, A., 2001. Cdc42 induces filopodia by promoting the formation of an IRSp53:Mena complex. Curr. Biol. 11, 1645–1655.
Kuhlman, P.A., Hughes, C.A., Bennett, V., Fowler, V.M., 1996. A new function for adducin. Calcium/calmodulin-regulated capping of the barbed ends of actin filaments. J. Biol. Chem. 271, 7986–7991.
Kuriu, T., Inoue, A., Bito, H., Sobue, K., Okabe, S., 2006. Differential control of postsynaptic density scaffolds via actin-dependent and -independent mechanisms. J. Neurosci. 26, 7693–7706.
Lai, K.O., Wong, A.S., Cheung, M.C., Xu, P., Liang, Z., Lok, K.C., Xie, H., Palko, M.E., Yung, W.H., Tessarollo, L., Cheung, Z.H., Ip, N.Y., 2012. TrkB phosphorylation by Cdk5 is required for activity-dependent structural plasticity and spatial memory. Nat. Neurosci. 15, 1506–1515.
Lamprecht, R., 1999. CREB: a message to remember. Cell. Mol. Life Sci. 55, 554–563.

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

Lamprecht, R., Farb, C.R., LeDoux, J.E., 2002. Fear memory formation involves p190 RhoGAP and ROCK proteins through a GRB2-mediated complex. Neuron 36, 727–738.
Lamprecht, R., LeDoux, J., 2004. Structural plasticity and memory. Nat. Rev. Neurosci. 5, 45–54.
Lamprecht, R., Farb, C.R., Rodrigues, S.M., LeDoux, J.E., 2006a. Fear conditioning drives profilin into amygdala dendritic spines. Nat. Neurosci. 9, 481–483.
Lamprecht, R., Margulies, D.S., Farb, C.R., Hou, M., Johnson, L.R., LeDoux, J.E., 2006b. Myosin light chain kinase regulates synaptic plasticity and fear learning in the lateral amygdala. Neuroscience 139, 821–829.
Landis, D.M., Hall, A.K., Weinstein, L.A., Reese, T.S., 1988. The organization of cytoplasm at the presynaptic active zone of a central nervous system synapse. Neuron 1, 201–209.
Lei, S., Czerwinska, E., Czerwinski, W., Walsh, M.P., MacDonald, J.F., 2001. Regulation of NMDA receptor activity by F-actin and myosin light chain kinase. J. Neurosci. 21, 8464–8472.
Letourneau, P.C., 2009. Actin in axons: stable scaffolds and dynamic filaments. Results Probl. Cell Differ. 48, 65–90.
Leuner, B., Falduto, J., Shors, T.J., 2003. Associative memory formation increases the observation of dendritic spines inb the hippocampus. J. Neurosci. 23, 659–665.
Li, Z., Van Aelst, L., Cline, H.T., 2000. Rho GTPases regulate distinct aspects of dendritic arbor growth in Xenopus central neurons in vivo. Nat. Neurosci. 3, 217–225.
Limouze, J., Straight, A.F., Mitchison, T., Sellers, J.R., 2004. Specificity of blebbistatin, an inhibitor of myosin II. J. Muscle Res. Cell Motil. 25, 337–341.
Lin, D.T., Makino, Y., Sharma, K., Hayashi, T., Neve, R., Takamiya, K., Huganir, R.L., 2009. Regulation of AMPA receptor extrasynaptic insertion by 4.1 N, phosphorylation and palmitoylation. Nat. Neurosci. 12, 879–887.
Lippi, G., Steinert, J.R., Marczylo, E.L., D'Oro, S., Fiore, R., Forsythe, I.D., Schratt, G., Zoli, M., Nicotera, P., Young, K.W., 2011. Targeting of the Arpc3 actin nucleation factor by miR-29a/b regulates dendritic spine morphology. J. Cell Biol. 194, 889–904.
Lisé, M.F., Wong, T.P., Trinh, A., Hines, R.M., Liu, L., Kang, R., Hines, D.J., Lu, J., Goldenring, J.R., Wang, Y.T., El-Husseini, A., 2006. Involvement of myosin Vb in glutamate receptor trafficking. J. Biol. Chem. 281, 3669–3678.
Luo, L., 2000. Rho GTPases in neuronal morphogenesis. Nat. Rev. Neurosci. 1, 173–180.
Luo, L., 2002. Actin cytoskeleton regulation in neuronal morphogenesis and structural plasticity. Annu. Rev. Cell Dev. Biol. 18, 601–635.
Lynch, M.A., 2004. Long-term potentiation and memory. Physiol. Rev. 84, 87–136.
Ma, X.M., Kiraly, D.D., Gaier, E.D., Wang, Y., Kim, E.J., Levine, E.S., Eipper, B.A., Mains, R.E., 2008. Kalirin-7 is required for synaptic structure and function. J. Neurosci. 28, 12368–12382.
Machesky, L.M., Insall, R.H., 1998. Scar1 and the related Wiskott–Aldrich syndrome protein, WASP, regulate the actin cytoskeleton through the Arp2/3 complex. Curr. Biol. 8, 1347–1356.
Maekawa, M., Ishizaki, T., Boku, S., Watanabe, N., Fujita, A., Iwamatsu, A., Obinata, T., Ohashi, K., Mizuno, K., Narumiya, S., 1999. Signaling from Rho to the actin cytoskeleton through protein kinases ROCK and LIM-kinase. Science 285, 895–898.
Mailleux, P., Takazawa, K., Erneux, C., Vanderhaeghen, J.J., 1991. Inositol 1,4,5-trisphosphate 3-kinase mRNA: high levels in the rat hippocampal CA1 pyramidal and dentate gyrus granule cells and in cerebellar Purkinje cells. J. Neurochem. 56, 345–347.
Maguschak, K.A., Ressler, K.J., 2008. β-Catenin is required for memory consolidation. Nat. Neurosci. 11, 1319–1326.
Malenka, R.C., Nicoll, R.A., 1999. Long-term potentiation – a decade of progress? Science 285, 1870–1874.
Mantzur, L., Joels, G., Lamprecht, R., 2009. Actin polymerization in lateral amygdala is essential for fear memory formation. Neurobiol. Learn. Mem. 91, 85–88.
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711.
Martinez, L.A., Klann, E., Tejada-Simon, M.V., 2007. Translocation and activation of Rac in the hippocampus during associative contextual fear learning. Neurobiol. Learn. Mem. 88, 104–113.
Martinez, L.A., Tejada-Simon, M.V., 2011. Pharmacological inactivation of the small GTPase Rac1 impairs long-term plasticity in the mouse hippocampus. Neuropharmacology 61, 305–312.
Matsuzaki, M., Honkura, N., Ellis-Davies, G.C., Kasai, H., 2004. Structural basis of long-term potentiation in single dendritic spines. Nature 429, 761–766.
Matsuo, N., Reijmers, L., Mayford, M., 2008. Spine-type-specific recruitment of newly synthesized AMPA receptors with learning. Science 319, 1104–1107.
Matsuoka, Y., Hughes, C.A., Bennett, V., 1996. Adducin regulation. Definition of the calmodulin-binding domain and sites of phosphorylation by protein kinases A and C. J. Biol. Chem. 271, 25157–25166.
Matsuoka, Y., Li, X., Bennett, V., 1998. Adducin is an in vivo substrate for protein kinase C: phosphorylation in the MARCKS-related domain inhibits activity in promoting spectrin-actin complexes and occurs in many cells, including dendritic spines of neurons. J. Cell Biol. 142, 485–497.
Matus, A., 2000. Actin-based plasticity in dendritic spines. Science 290, 754–758.
McKernan, M.G., Shinnick-Gallagher, P., 1997. Fear conditioning induces a lasting potentiation of synaptic currents in vitro. Nature 390, 607–611.
McNair, K., Spike, R., Guilding, C., Prendergast, G.C., Stone, T.W., Cobb, S.R., Morris, B.J., 2010. A role for RhoB in synaptic plasticity and the regulation of neuronal morphology. J. Neurosci. 30, 3508–3517.
McPherson, C.E., Eipper, B.A., Mains, R.E., 2004. Kalirin expression is regulated by multiple promoters. J. Mol. Neurosci. 22, 51–62.
Meng, Y., Zhang, Y., Tregoubov, V., Janus, C., Cruz, L., Jackson, M., Lu, W.Y., MacDonald, J.F., Wang, J.Y., Falls, D.L., Jia, Z., 2002. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron 35, 121–133.
Menna, E., Zambetti, S., Morini, R., Donzelli, A., Disanza, A., Calvigioni, D., Braida, D., Nicolini, C., Orlando, M., Fossati, G., Cristina Regondi, M., Pattini, L., Frassoni, C., Francolini, M., Scita, G., Sala, M., Fahnestock, M., Matteoli, M., 2013. Eps8 controls dendritic spine density and synaptic plasticity through its actin-capping activity. EMBO J. 32, 1730–1744.
Mikati, M.A., Grintsevich, E.E., Reisler, E., 2013. Drebrin-induced stabilization of actin filaments. J. Biol. Chem 288, 19926–19938.
Miki, H., Yamaguchi, H., Suetsugu, S., Takenawa, T., 2000. IRSp53 is an essential intermediate between Rac and WAVE in the regulation of membrane ruffling. Nature 408, 732–735.
Mische, S.M., Mooseker, M.S., Morrow, J.S., 1987. Erythrocyte adducin: a calmodulin-regulated actin-bundling protein that stimulates spectrin-actin binding. J. Cell Biol. 105, 2837–2845.
Mochida, S., Kobayashi, H., Matsuda, Y., Yuda, Y., Muramoto, K., Nonomura, Y., 1994. Myosin II is involved in transmitter release at synapses formed between rat sympathetic neurons in culture. Neuron 13, 1131–1142.
Morishita, W., Marie, H., Malenka, R.C., 2005. Distinct triggering and expression mechanisms underlie LTD of AMPA and NMDA synaptic responses. Nat. Neurosci. 8, 1043–1050.
Morris, R.G., Anderson, E., Lynch, G.S., Baudry, M., 1986. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319, 774–776.
Motanis, H., Maroun, M., 2012. Differential involvement of protein synthesis and actin rearrangement in the reacquisition of contextual fear conditioning. Hippocampus 22, 494–500.
Muller, J., Corodimas, K.P., Fridel, Z., LeDoux, J.E., 1997. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. Behav. Neurosci. 111, 683–691.
Mullins, R., Heuser, J., Pollard, T., 1998. The interaction of Arp2/3 complex with actin: nucleation, high affinity pointed end capping, and formation of branching networks of filaments. Proc. Natl. Acad. Sci. U.S.A. 95, 6181–6186.
Murakoshi, H., Wang, H., Yasuda, R., 2011. Local, persistent activation of Rho GTPases during plasticity of single dendritic spines. Nature 472, 100–104.
Nakagawa, H., Miki, H., Nozumi, M., Takenawa, T., Miyamoto, S., Wehland, J., Small, J.V., 2003. IRSp53 is colocalised with WAVE2 at the tips of protruding lamellipodia and filopodia independently of Mena. J. Cell Sci. 116, 2577–2583.
Nakamura, Y., Wood, C.L., Patton, A.P., Jaafari, N., Henley, J.M., Mellor, J.R., Hanley, J.G., 2011. PICK1 inhibition of the Arp2/3 complex controls dendritic spine size and synaptic plasticity. EMBO J. 30, 719–730.
Nakanishi, H., Obaishi, H., Satoh, A., Wada, M., Mandai, K., Satoh, K., Nishioka, H., Matsuura, Y., Mizoguchi, A., Takai, Y., 1997. Neurabin: a novel neural tissue-specific actin filament-binding protein involved in neurite formation. J. Cell Biol. 139, 951–961.
Nakazawa, T., Kuriu, T., Tezuka, T., Umemori, H., Okabe, S., Yamamoto, T., 2008. Regulation of dendritic spine morphology by an NMDA receptor-associated Rho GTPase-activating protein, p250GAP. J. Neurochem. 105, 1384–1393.
Nedelescu, H., Kelso, C.M., Lázaro-Muñoz, G., Purpura, M., Cain, C.K., Ledoux, J.E., Aoki, C., 2010. Endogenous GluR1-containing AMPA receptors translocate to asymmetric synapses in the lateral amygdala during the early phase of fear memory formation: an electron microscopic immunocytochemical study. J. Comp. Neurol. 518, 4723–4739.
Nelson, B.S., Witty, C.F., Williamson, E.A., Daniel, J.M., 2012. A role for hippocampal actin rearrangement in object placement memory in female rats. Neurobiol. Learn. Mem. 98, 284–290.
Nelson, J.C., Stavoe, A.K., Colón-Ramos, D.A., 2013. The actin cytoskeleton in presynaptic assembly. Cell Adhes. Migr. 7, 379–387.
Nekrasova, T., Jobes, M.L., Ting, J.H., Wagner, G.C., Minden, A., 2008. Targeted disruption of the Pak5 and Pak6 genes in mice leads to deficits in learning and locomotion. Dev. Biol. 322, 95–108.
Neuhoff, H., Sassoè-Pognetto, M., Panzanelli, P., Maas, C., Witke, W., Kneussel, M., 2005. The actin-binding protein profilin I is localized at synaptic sites in an activity-regulated manner. Eur. J. Neurosci. 21, 15–25.
Newey, S.E., Velamoor, V., Govek, E.E., Van Aelst, L., 2005. Rho GTPases, dendritic structure, and mental retardation. J. Neurobiol. 64, 58–74.
Newpher, T.M., Ehlers, M.D., 2009. Spine microdomains for postsynaptic signaling and plasticity. Trends Cell Biol. 19, 218–222.
Niisato, K., Fujikawa, A., Komai, S., Shintani, T., Watanabe, E., Sakaguchi, G., Katsuura, G., Manabe, T., Noda, M., 2005. Age-dependent enhancement of hippocampal long-term potentiation and impairment of spatial learning through the Rho-associated kinase pathway in protein tyrosine phosphatase receptor type Z-deficient mice. J. Neurosci. 25, 1081–1088.
Nimchinsky, E.A., Sabatini, B.L., Svoboda, K., 2002. Structure and function of dendritic spines. Annu. Rev. Physiol. 64, 313–353.
Nishiwaki, T., Maeda, N., Noda, M., 1998. Characterization and developmental regulation of proteoglycan-type protein tyrosine phosphatase ζ/RPTPβ isoforms. J. Biochem. 123, 458–467.
Oh, D., Han, S., Seo, J., Lee, J.R., Choi, J., Groffen, J., Kim, K., Cho, Y.S., Choi, H.S., Shin, H., Woo, J., Won, H., Park, S.K., Kim, S.Y., Jo, J., Whitcomb, D.J., Cho, K., Kim, H., Bae, Y.C., Heisterkamp, N., Choi, S.Y., Kim, E., 2010. Regulation of synaptic Rac1

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

activity, long-term potentiation maintenance, and learning and memory by BCR and ABR Rac GTPase-activating proteins. J. Neurosci. 30, 14134–14144.
Okamoto, K., Nagai, T., Miyawaki, A., Hayashi, Y., 2004. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat. Neurosci. 7, 1104–1112.
O'Kane, E.M., Stone, T.W., Morris, B.J., 2004. Increased long-term potentiation in the CA1 region of rat hippocampus via modulation of GTPase signalling or inhibition of Rho kinase. Neuropharmacology 46, 879–887.
Osterweil, E., Wells, D.G., Mooseker, M.S., 2005. A role for myosin VI in postsynaptic structure and glutamate receptor endocytosis. J. Cell Biol. 168, 329–338.
Ostroff, L.E., Cain, C.K., Bedont, J., Monfils, M.H., Ledoux, J.E., 2010. Fear and safety learning differentially affect synapse size and dendritic translation in the lateral amygdala. Proc. Natl. Acad. Sci. U.S.A. 107, 9418–9423.
Ota, K.T., Monsey, M.S., Wu, M.S., Schafe, G.E., 2010. Synaptic plasticity and NO-cGMP-PKG signaling regulate pre- and postsynaptic alterations at rat lateral amygdala synapses following fear conditioning. PLoS ONE 5, e11236.
Pavlov, I.P., 1927. Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Oxford Univ. Press, London.
Penzes, P., Johnson, R.C., Alam, M.R., Kambampati, V., Mains, R.E., Eipper, B.A., 2000. An isoform of kalirin, a brain-specific GDP/GTP exchange factor, is enriched in the postsynaptic density fraction. J. Biol. Chem. 275, 6395–6403.
Penzes, P., Johnson, R.C., Sattler, R., Zhang, X., Huganir, R.L., Kambampati, V., Mains, R.E., Eipper, B.A., 2001. The neuronal Rho-GEF Kalirin-7 interacts with PDZ domain-containing proteins and regulates dendritic morphogenesis. Neuron 29, 229–242.
Penzes, P., Beeser, A., Chernoff, J., Schiller, M.R., Eipper, B.A., Mains, R.E., Huganir, R.L., 2003. Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. Neuron 37, 263–274.
Pilo Boyl, P., Di Nardo, A., Mulle, C., Sassoè-Pognetto, M., Panzanelli, P., Mele, A., Kneussel, M., Costantini, V., Perlas, E., Massimi, M., Vara, H., Giustetto, M., Witke, W., 2007. Profilin2 contributes to synaptic vesicle exocytosis, neuronal excitability, and novelty-seeking behavior. EMBO J. 26, 2991–3002.
Polepalli, J.S., Sullivan, R.K., Yanagawa, Y., Sah, P., 2010. A specific class of interneuron mediates inhibitory plasticity in the lateral amygdala. J. Neurosci. 30, 14619–14629.
Pollard, T., 2007. Regulation of actin filament assembly by Arp2/3 complex and formins. Annu. Rev. Biophys. Biomol. Struct. 36, 451–477.
Pollitt, A.Y., Insall, R.H., 2009. WASP and SCAR/WAVE proteins: the drivers of actin assembly. J. Cell Sci. 122, 2575–2578.
Polo-Parada, L., Bose, C.M., Landmesser, L.T., 2001. Alterations in transmission, vesicle dynamics, and transmitter release machinery at NCAM-deficient neuromuscular junctions. Neuron 32, 815–828.
Porro, F., Rosato-Siri, M., Leone, E., Costessi, L., Iaconcig, A., Tongiorgi, E., Muro, A.F., 2010. beta-adducin (Add2) KO mice show synaptic plasticity, motor coordination and behavioral deficits accompanied by changes in the expression and phosphorylation levels of the alpha- and gamma-adducin subunits. Genes Brain Behav. 9, 84–96.
Pontrello, C.G., Sun, M.Y., Lin, A., Fiacco, T.A., DeFea, K.A., Ethell, I.M., 2012. Cofilin under control of β-arrestin-2 in NMDA-dependent dendritic spine plasticity, long-term depression (LTD), and learning. Proc. Natl. Acad. Sci. U.S.A. 109, 442–451.
Prekeris, R., Terrian, D.M., 1997. Brain myosin V is a synaptic vesicle-associated motor protein: evidence for a Ca^{2+}-dependent interaction with the synaptobrevin-synaptophysin complex. J. Cell Biol. 137, 1589–1601.
Rabenstein, R.L., Addy, N.A., Caldarone, B.J., Asaka, Y., Gruenbaum, L.M., Peters, L.L., Gilligan, D.M., Fitzsimonds, R.M., Picciotto, M.R., 2005. Impaired synaptic plasticity and learning in mice lacking beta-adducin, an actin-regulating protein. J. Neurosci. 25, 2138–2145.
Rácz, B., Weinberg, R.J., 2008. Organization of the Arp2/3 complex in hippocampal spines. J. Neurosci. 28, 5654–5659.
Radley, J.J., Johnson, L.R., Janssen, W.G., Martino, J., Lamprecht, R., Hof, P.R., LeDoux, J.E., Morrison, J.H., 2006. Associative Pavlovian conditioning leads to an increase in spinophilin-immunoreactive dendritic spines in the lateral amygdala. Eur. J. Neurosci. 24, 876–884.
Ramachandran, B., Frey, J.U., 2009. Interfering with the actin network and its effect on long-term potentiation and synaptic tagging in hippocampal CA1 neurons in slices in vitro. J. Neurosci. 29, 12167–12173.
Ramakers, G.J., Avci, B., van Hulten, P., van Ooyen, A., van Pelt, J., Pool, C.W., Lequin, M.B., 2001. The role of calcium signaling in early axonal and dendritic morphogenesis of rat cerebral cortex neurons under non-stimulated growth conditions. Brain Res. Dev. Brain Res. 126, 163–172.
Rehberg, K., Bergado-Acosta, J.R., Koch, J.C., Stork, O., 2010. Disruption of fear memory consolidation and reconsolidation by actin filament arrest in the basolateral amygdala. Neurobiol. Learn. Mem. 94, 117–126.
Renner, M., Choquet, D., Triller, A., 2009. Control of the postsynaptic membrane viscosity. J. Neurosci. 29, 2926–2937.
Rescorla, R.A., 1996. Preservation of Pavlovian association through extinction. Q. J. Exp. Psychol. 49B, 245–258.
Restivo, L., Vetere, G., Bontempi, B., Ammassari-Teule, M., 2009. The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex. J. Neurosci. 29, 8206–8214.
Rex, C.S., Chen, L.Y., Sharma, A., Liu, J., Babayan, A.H., Gall, C.M., Lynch, G., 2009. Different Rho GTPase-dependent signaling pathways initiate sequential steps in the consolidation of long-term potentiation. J. Cell Biol. 186, 85–97.
Rex, C.S., Gavin, C.F., Rubio, M.D., Kramar, E.A., Chen, L.Y., Jia, Y., Huganir, R.L., Muzyczka, N., Gall, C.M., Miller, C.A., Lynch, G., Rumbaugh, G., 2010. Myosin IIb regulates actin dynamics during synaptic plasticity and memory formation. Neuron 67, 603–617.
Riento, K., Ridley, A.J., 2003. Rocks: multifunctional kinases in cell behaviour. Nat. Rev. Mol. Cell Biol. 4, 446–456.
Roberts, T.F., Tschida, K.A., Klein, M.E., Mooney, R., 2010. Rapid spine stabilization and synaptic enhancement at the onset of behavioural learning. Nature 463, 948–952.
Rodal, A.A., Sokolova, O., Robins, D.B., Daugherty, K.M., Hippenmeyer, S., Riezman, H., Grigorieff, N., Goode, B.L., 2005. Conformational changes in the Arp2/3 complex leading to actin nucleation. Nat. Struct. Mol. Biol. 12, 26–31.
Rodrigues, S.M., Schafe, G.E., LeDoux, J.E., 2004. Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. Neuron 44, 75–91.
Rogan, M.T., LeDoux, J.E., 1995. LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. Neuron 15, 127–136.
Rogan, M.T., Staubli, U.V., LeDoux, J.E., 1997. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390, 604–607.
Roof, R.W., Dukes, B.D., Chang, J.H., Parsons, S.J., 2000. Phosphorylation of the p190 RhoGAP N-terminal domain by c-Src results in a loss of GTP binding activity. FEBS Lett. 472, 117–121.
Rotty, J.D., Wu, C., Bear, J.E., 2013. New insights into the regulation and cellular functions of the ARP2/3 complex. Nat. Rev. Mol. Cell Biol. 14, 7–12.
Rozic, G., Lupowitz, Z., Piontkewitz, Y., Zisapel, N., 2011. Dynamic changes in neurexins' alternative splicing: role of Rho-associated protein kinases and relevance to memory formation. PLoS ONE 6, e18579.
Ruediger, S., Vittori, C., Bednarek, E., Genoud, C., Strata, P., Sacchetti, B., Caroni, P., 2011. Learning-related feedforward inhibitory connectivity growth required for memory precision. Nature 473, 514–518.
Rumpel, S., LeDoux, J., Zador, A., Malinow, R., 2005. Postsynaptic receptor trafficking underlying a form of associative learning. Science 308, 83–88.
Rust, M.B., Gurniak, C.B., Renner, M., Vara, H., Morando, L., Görlich, A., Sassoè-Pognetto, M., Banchaabouchi, M.A., Giustetto, M., Triller, A., Choquet, D., Witke, W., 2010. Learning, AMPA receptor mobility and synaptic plasticity depend on n-cofilin-mediated actin dynamics. EMBO J. 29, 1889–1902.
Ryan, T.A., 1999. Inhibitors of myosin light chain kinase block synaptic vesicle pool mobilization during action potential firing. J. Neurosci. 19, 1317–1323.
Saar, D., Reuveni, I., Barkai, E., 2012. Mechanisms underlying rule learning-induced enhancement of excitatory and inhibitory synaptic transmission. J. Neurophysiol. 107, 1222–1229.
Sacchetti, B., Ambrogi Lorenzini, C., Baldi, E., Bucherelli, C., Roberto, M., Tassoni, G., Brunelli, M., 2001. Long-lasting hippocampal potentiation and contextual memory consolidation. Eur. J. Neurosci. 13, 2291–2298.
Sacchetti, B., Lorenzini, C.A., Baldi, E., Bucherelli, C., Roberto, M., Tassoni, G., Brunelli, M., 2002. Time-dependent inhibition of hippocampal LTP in vitro following contextual fear conditioning in the rat. Eur. J. Neurosci. 15, 143–150.
Sananbenesi, F., Fischer, A., Wang, X., Schrick, C., Neve, R., Radulovic, J., Tsai, L.H., 2007. A hippocampal Cdk5 pathway regulates extinction of contextual fear. Nat. Neurosci. 10, 1012–1019.
Saneyoshi, T., Wayman, G., Fortin, D., Davare, M., Hoshi, N., Nozaki, N., Natsume, T., Soderling, T.R., 2008. Activity-dependent synaptogenesis: regulation by a CaM-kinase kinase/CaM-kinase I/betaPIX signaling complex. Neuron 57, 94–107.
Sankaranarayanan, S., Atluri, P.P., Ryan, T.A., 2003. Actin has a molecular scaffolding, not propulsive, role in presynaptic function. Nat. Neurosci. 6, 127–135.
Sarrouilhe, D., di Tommaso, A., Métayé, T., Ladeveze, V., 2006. Spinophilin: from partners to functions. Biochimie 88, 1099–1113.
Satoh, A., Nakanishi, H., Obaishi, H., Wada, M., Takahashi, K., Satoh, K., Hirao, K., Nishioka, H., Hata, Y., Mizoguchi, A., Takai, Y., 1998. Neurabin-II/spinophilin. An actin filament-binding protein with one pdz domain localized at cadherin-based cell-cell adhesion sites. J. Biol. Chem. 273, 3470–3475.
Savelieva, K.V., Rajan, I., Baker, K.B., Vogel, P., Jarman, W., Allen, M., Lanthorn, T.H., 2008. Learning and memory impairment in Eph receptor A6 knockout mice. Neurosci. Lett. 438, 205–209.
Schratt, G.M., Tuebing, F., Nigh, E.A., Kane, C.G., Sabatini, M.E., Kiebler, M., Greenberg, M.E., 2006. A brain-specific microRNA regulates dendritic spine development. Nature 439, 283–289.
Schrick, C., Fischer, A., Srivastava, D.P., Tronson, N.C., Penzes, P., Radulovic, J., 2007. N-cadherin regulates cytoskeletally associated IQGAP1/ERK signaling and memory formation. Neuron 55, 786–798.
Schroeder, B.W., Shinnick-Gallagher, P., 2004. Fear memories induce a switch in stimulus response and signaling mechanisms for long-term potentiation in the lateral amygdala. Eur. J. Neurosci. 20, 549–556.
Schroeder, B.W., Shinnick-Gallagher, P., 2005. Fear learning induces persistent facilitation of amygdala synaptic transmission. Eur. J. Neurosci. 22, 1775–1783.
Schubert, V., Da Silva, J.S., Dotti, C.G., 2006. Localized recruitment and activation of RhoA underlies dendritic spine morphology in a glutamate receptor-dependent manner. J. Cell Biol. 172, 453–467.
Schubert, V., Dotti, C.G., 2007. Transmitting on actin: synaptic control of dendritic architecture. J. Cell Sci. 120, 205–212.
Schulz, T.W., Nakagawa, T., Licznerski, P., Pawlak, V., Kolleker, A., Rozov, A., Kim, J., Dittgen, T., Köhr, G., Sheng, M., Seeburg, P.H., Osten, P., 2004. Actin/alpha-actinin-dependent transport of AMPA receptors in dendritic spines: role of the PDZ-LIM protein RIL. J. Neurosci. 24, 8584–8594.
Sekino, Y., Kojima, N., Shirao, T., 2007. Role of actin cytoskeleton in dendritic spine morphogenesis. Neurochem. Int. 51, 92–104.

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001

Shamah, S.M., Lin, M.Z., Goldberg, J.L., Estrach, S., Sahin, M., Hu, L., Bazalakova, M., Neve, R.L., Corfas, G., Debant, A., Greenberg, M.E., 2001. EphA receptors regulate growth cone dynamics through the novel guanine nucleotide exchange factor ephexin. Cell 105, 233–244.
Shen, L., Liang, F., Walensky, L.D., Huganir, R.L., 2000. Regulation of AMPA receptor GluR1 subunit surface expression by a 4.1N-linked actin cytoskeletal association. J. Neurosci. 20, 7932–7940.
Shuai, Y., Lu, B., Hu, Y., Wang, L., Sun, K., Zhong, Y., 2010. Forgetting is regulated through Rac activity in Drosophila. Cell 140, 579–589.
Shuai, Y., Hu, Y., Qin, H., Campbell, R.A., Zhong, Y., 2011. Distinct molecular underpinnings of Drosophila olfactory trace conditioning. Proc. Natl. Acad. Sci. U.S.A. 108, 20201–20206.
Shupliakov, O., Bloom, O., Gustafsson, J.S., Kjaerulff, O., Low, P., Tomilin, N., Pieribone, V.A., Greengard, P., Brodin, L., 2002. Impaired recycling of synaptic vesicles after acute perturbation of the presynaptic actin cytoskeleton. Proc. Natl. Acad. Sci. U.S.A. 99, 14476–14481.
Soderling, S.H., Binns, K.L., Wayman, G.A., Davee, S.M., Ong, S.H., Pawson, T., Scott, J.D., 2002. The WRP component of the WAVE-1 complex attenuates Rac-mediated signalling. Nat. Cell Biol. 4, 970–975.
Soderling, S.H., Langeberg, L.K., Soderling, J.A., Davee, S.M., Simerly, R., Raber, J., Scott, J.D., 2003. Loss of WAVE-1 causes sensorimotor retardation and reduced learning and memory in mice. Proc. Natl. Acad. Sci. U.S.A. 100, 1723–1728.
Soderling, S.H., Guire, E.S., Kaech, S., White, J., Zhang, F., Schutz, K., Langeberg, L.K., Banker, G., Raber, J., Scott, J.D., 2007. A WAVE-1 and WRP signaling complex regulates spine density, synaptic plasticity, and memory. J. Neurosci. 27, 355–365.
Somlyo, A.P., Somlyo, A.V., 2003. Ca^{2+} sensitivity of smooth muscle and nonmuscle myosin II: modulated by G proteins, kinases, and myosin phosphatase. Physiol. Rev. 83, 1325–1358.
Stafstrom-Davis, C.A., Ouimet, C.C., Feng, J., Allen, P.B., Greengard, P., Houpt, T.A., 2001. Impaired conditioned taste aversion learning in spinophilin knockout mice. Learn. Mem. 8, 272–278.
Stamatakou, E., Marzo, A., Gibb, A., Salinas, P.C., 2013. Activity-dependent spine morphogenesis: a role for the actin-capping protein Eps8. J. Neurosci. 33, 2661–2670.
Star, E.N., Kwiatkowski, D.J., Murthy, V.N., 2002. Rapid turnover of actin in dendritic spines and its regulation by activity. Nat. Neurosci. 5, 239–246.
Stossel, T.P., Condeelis, J., Cooley, L., Hartwig, J.H., Noegel, A., Schleicher, M., Shapiro, S.S., 2001. Filamins as integrators of cell mechanics and signalling. Nat. Rev. Mol. Cell. Biol. 2, 138–145.
Suetsugu, S., Kurisu, S., Oikawa, T., Yamazaki, D., Oda, A., Takenawa, T., 2006. Optimization of WAVE2 complex-induced actin polymerization by membrane-bound IRSp53, PIP(3), and Rac. J. Cell Biol. 173, 571–585.
Sumi, T., Matsumoto, K., Takai, Y., Nakamura, T., 1999. Cofilin phosphorylation and actin cytoskeletal dynamics regulated by rho- and Cdc42-activated LIM-kinase 2. J. Cell Biol. 147, 1519–1532.
Suriyapperuma, S.P., Lozovatsky, L., Ciciotte, S.L., Peters, L.L., Gilligan, D.M., 2000. The mouse adducin gene family: alternative splicing and chromosomal localization. Mamm. Genome 11, 16–23.
Suzuki, A., Stern, S.A., Bozdagi, O., Huntley, G.W., Walker, R.H., Magistretti, P.J., Alberini, C.M., 2011. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144, 810–823.
Sweetat, S., Rosenblum, K., Lamprecht, R., 2012. Rho-associated kinase in the gustatory cortex is involved in conditioned taste aversion memory formation but not in memory retrieval or relearning. Neurobiol. Learn. Mem. 97, 1–6.
Tada, T., Sheng, M., 2006. Molecular mechanisms of dendritic spine morphogenesis. Curr. Opin. Neurobiol. 16, 95–101.
Takenawa, T., Suetsugu, S., 2007. The WASP-WAVE protein network: connecting the membrane to the cytoskeleton. Nat. Rev. Mol. Cell Biol. 8, 37–48.
Tamura, H., Fukada, M., Fujikawa, A., Noda, M., 2006. Protein tyrosine phosphatase receptor type Z is involved in hippocampus-dependent memory formation through dephosphorylation at Y1105 on p190 RhoGAP. Neurosci. Lett. 399, 33–38.
Tan, E.C., Leung, T., Manser, E., Lim, L., 1993. The human active breakpoint cluster region-related gene encodes a brain protein with homology to guanine nucleotide exchange proteins and GTPase-activating proteins. J. Biol. Chem. 268, 27291–27298.
Tejada-Simon, M.V., Villasana, L.E., Serrano, F., Klann, E., 2006. NMDA receptor activation induces translocation and activation of Rac in mouse hippocampal area CA1. Biochem. Biophys. Res. Commun. 343, 504–512.
Tolias, K.F., Bikoff, J.B., Burette, A., Paradis, S., Harrar, D., Tavazoie, S., Weinberg, R.J., Greenberg, M.E., 2005. The Rac1-GEF Tiam1 couples the NMDA receptor to the activity-dependent development of dendritic arbors and spines. Neuron 45, 525–538.
Tolias, K.F., Duman, J.G., Um, K., 2011. Control of synapse development and plasticity by Rho GTPase regulatory proteins. Prog. Neurobiol. 94, 133–148.
Tsien, J.Z., Huerta, P.T., Tonegawa, S., 1996. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87, 1327–1338.
Tsien, J.Z., 2000. Linking Hebb's coincidence-detection to memory formation. Curr. Opin. Neurobiol 10, 266–273.
Tsvetkov, E., Carlezon, W.A., Benes, F.M., Kandel, E.R., Bolshakov, V.Y., 2002. Fear conditioning occludes LTP-induced presynaptic enhancement of synaptic transmission in the cortical pathway to the lateral amygdala. Neuron 34, 289–300.
Udo, H., Jin, I., Kim, J.H., Li, H.L., Youn, T., Hawkins, R.D., Kandel, E.R., Bailey, C.H., 2005. Serotonin-induced regulation of the actin network for learning-related synaptic growth requires Cdc42, N-WASP, and PAK in Aplysia sensory neurons. Neuron 45, 887–901.
Vanleeuwen, J.E., Penzes, P., 2012. Long-term perturbation of spine plasticity results in distinct impairments of cognitive function. J. Neurochem. 123, 781–789.
Van Troys, M., Huyck, L., Leyman, S., Dhaese, S., Vandekerkhove, J., Ampe, C., 2008. Ins and outs of ADF/cofilin activity and regulation. Eur. J. Cell Biol. 87, 649–667.
Vetere, G., Restivo, L., Cole, C.J., Ross, P.J., Ammassari-Teule, M., Josselyn, S.A., Frankland, P.W., 2011. Spine growth in the anterior cingulate cortex is necessary for the consolidation of contextual fear memory. Proc. Natl. Acad. Sci. U.S.A. 108, 8456–8460.
Volkmann, N., Amann, K.J., Stoilova-McPhie, S., Egile, C., Winter, D.C., Hazelwood, L., Heuser, J.E., Li, R., Pollard, T.D., Hanein, D., 2001. Structure of Arp2/3 complex in its activated state and in actin filament branch junctions. Science 293, 2456–2459.
Voncken, J.W., van Schaick, H., Kaartinen, V., Deemer, K., Coates, T., Landing, B., Pattengale, P., Dorseuil, O., Bokoch, G.M., Groffen, J., 1995. Increased neutrophil respiratory burst in bcr-null mutants. Cell 80, 719–728.
Vukojevic, V., Gschwind, L., Vogler, C., Demougin, P., de Quervain, D.J., Papassotiropoulos, A., Stetak, A., 2012. A role for α-adducin (ADD-1) in nematode and human memory. EMBO J. 31, 1453–1466.
Wang, X.H., Zheng, J.Q., Poo, M.M., 1996. Effects of cytochalasin treatment on short-term synaptic plasticity at developing neuromuscular junctions in frogs. J. Physiol. 491, 187–195.
Wang, H.G., Lu, F.M., Jin, I., Udo, H., Kandel, E.R., de Vente, J., Walter, U., Lohmann, S.M., Hawkins, R.D., Antonova, I., 2005. Presynaptic and postsynaptic roles of NO, cGK, and RhoA in long-lasting potentiation and aggregation of synaptic proteins. Neuron 45, 389–403.
Wang, Z., Edwards, J.G., Riley, N., Provance Jr., D.W., Karcher, R., Li, X.D., Davison, I.G., Ikebe, M., Mercer, J.A., Kauer, J.A., Ehlers, M.D., 2008. Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity. Cell 135, 535–548.
Wang, Y., Dong, Q., Xu, X.F., Feng, X., Xin, J., Wang, D.D., Yu, H., Tian, T., Chen, Z.Y., 2013. Phosphorylation of cofilin regulates extinction of conditioned aversive memory via AMPAR trafficking. J. Neurosci. 33, 6423–6433.
Watanabe, M., Nomura, K., Ohyama, A., Ishikawa, R., Komiya, Y., Hosaka, K., Yamauchi, E., Taniguchi, H., Sasakawa, N., Kumakura, K., Ushiki, T., Sato, O., Ikebe, M., Igarashi, M., 2005. Myosin-Va regulates exocytosis through the submicromolar Ca^{2+}-dependent binding of syntaxin-1A. Mol. Biol. Cell 16, 4519–4530.
Wegner, A.M., Nebhan, C.A., Hu, L., Majumdar, D., Meier, K.M., Weaver, A.M., Webb, D.J., 2008. N-wasp and the arp2/3 complex are critical regulators of actin in the development of dendritic spines and synapses. J. Biol. Chem. 283, 15912–15920.
Witke, W., 2004. The role of profilin complexes in cell motility and other cellular processes. Trends Cell Biol. 14, 461–469.
Whitlock, J.R., Heynen, A.J., Shuler, M.G., Bear, M.F., 2006. Learning induces long-term potentiation in the hippocampus. Science 313, 1093–1097.
Wu, L.J., Ren, M., Wang, H., Kim, S.S., Cao, X., Zhuo, M., 2008. Neurabin contributes to hippocampal long-term potentiation and contextual fear memory. PLoS ONE 3, e1407.
Xiao, M.Y., Zhou, Q., Nicoll, R.A., 2001. Metabotropic glutamate receptor activation causes a rapid redistribution of AMPA receptors. Neuropharmacology 41, 664–671.
Xie, Z., Srivastava, D.P., Photowala, H., Kai, L., Cahill, M.E., Woolfrey, K.M., Shum, C.Y., Surmeier, D.J., Penzes, P., 2007. Kalirin-7 controls activity-dependent structural and functional plasticity of dendritic spines. Neuron 56, 640–656.
Xie, Z., Cahill, M.E., Radulovic, J., Wang, J., Campbell, S.L., Miller, C.A., Sweatt, J.D., Penzes, P., 2011. Hippocampal phenotypes in kalirin-deficient mice. Mol. Cell Neurosci. 46, 45–54.
Yeh, S.H., Mao, S.C., Lin, H.C., Gean, P.W., 2006. Synaptic expression of glutamate receptor after encoding of fear memory in the rat amygdala. Mol. Pharmacol. 69, 299–308.
Yamashiro, S., Gokhin, D.S., Kimura, S., Nowak, R.B., Fowler, V.M., 2012. Tropomodulins: pointed-end capping proteins that regulate actin filament architecture in diverse cell types. Cytoskeleton 69, 337–370.
Yang, N., Higuchi, O., Ohashi, K., Nagata, K., Wada, A., Kangawa, K., Nishida, E., Mizuno, K., 1998. Cofilin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization. Nature 393, 809–812.
Young, E.J., Aceti, M., Griggs, E.M., Fuchs, R.A., Zigmond, Z., Rumbaugh, G., Miller, C.A., 2014. Selective, retrieval-independent disruption of methamphetamine-associated memory by actin depolymerization. Biol. Psychiatry 75, 96–104.
Zhou, Q., Xiao, M., Nicoll, R.A., 2001. Contribution of cytoskeleton to the internalization of AMPA receptors. Proc. Natl. Acad. Sci. U.S.A. 98, 1261–1266.
Zhou, F.Q., Waterman-Storer, C.M., Cohan, C.S., 2002. Focal loss of actin bundles causes microtubule redistribution and growth cone turning. J. Cell Biol. 157, 839–849.
Zhou, Q., Homma, K.J., Poo, M.M., 2004. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 44, 749–757.
Zhou, Z., Hu, J., Passafaro, M., Xie, W., Jia, Z., 2011. GluA2 (GluR2) regulates metabotropic glutamate receptor-dependent long-term depression through N-cadherin-dependent and cofilin-mediated actin reorganization. J. Neurosci. 31, 819–833.

Please cite this article in press as: Lamprecht, R., The actin cytoskeleton in memory formation. Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2014.02.001