Chapter 4
Neuropsin-Dependent and -Independent Synaptic Tagging and Modulation of Long-Term Potentiation: A Quest for the Associated Signaling Pathway(s)

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Abstract Synaptic tagging is plausible hypothesis that can potentially explain relational memory. However, it has not yet been cleared why and how the tagged synapses can be distinguished from the other non-activated synapses. Early-phase long-term potentiation (E-LTP)-related signaling molecules and intracellular molecular trafficking for capturing these toward tagged synapses have been considered as essential for synaptic tagging apparatus. In this chapter, we will describe a new mechanism of synaptic tagging which shares the common set of E-LTP induction mechanisms as above; that is, the E-LTP-specific proteolysis by neuropsin, an extracellular serine protease, is involved in neuropsin-dependent form of synaptic tagging.

Keywords E-LTP • Gate keepers • Extracellular • Neuropsin • NRG1 • ErbB4 • CaMKII • β1 integrin • LVDCC

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4.1 Introduction

Relational memory refers to the postulated role of the hippocampus in forming a collective representation of the various aspects of an experience. Thus, relational memory allows an individual who has experienced a traumatic event (e.g., a traffic accident) to remember even the most trivial details from the scene, as well as their spatial, sequential, and causative interconnections. This process permits the consolidation of signals from a number of weakly stimulated synapses into a single, sometimes unforgettable memory. However, little is known about the neural mechanism(s) underlying relational memory.

Synaptic tagging is a plausible hypothesis that can potentially explain relational memory. In 1997, Frey and Morris presented the hypothesis that active synapses are marked with a tag(s), and that newly synthesized, plasticity-related proteins (PRPs) must be targeted into the tagged synapses for prolongation of the potentiation state (Frey and Morris 1997). Because a weak synaptic stimulation is thought to produce a tag only at a single specific synapse and not to generate PRPs, a coordinated strong stimulation of a remote synapse arising from many weakly stimulated synapses is required to induce the production of new PRPs. These PRPs must then be transported into additional, specifically tagged synapses for the persistence of signal transmission between neurons. Therefore, the capturing and subsequent stabilization of new PRPs (such as the subunits of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor) at the tagged postsynapses are both essential for prolonged synaptic potentiation.

General intracellular signaling molecules have recently been considered as candidate molecular components of synaptic tagging apparatus (including those involved in the capture of PRPs) (Navakkode et al. 2005; Huang et al. 2006a; Sajikumar et al. 2007; Lu et al. 2011). However, extracellular molecules have not heretofore been taken into account as participants in synaptic tagging mechanisms. We now speculate that weak synaptic stimulation affords some initial change in extracellular matrix molecules and/or the extracellular domain of transmembrane signaling molecules found on the surface of the postsynaptic neuron, and that the resultant outside-in signaling permits PRP capture into the tagged dendritic spines. To explore this hypothesis, we focused on an established type of weak electrical stimulation, the single-pulse train (100 Hz, 1 s). The single-pulse train evokes only the early phase of long-term potentiation (E-LTP), lasting 1–3 h, and therefore provides a model of weak synaptic transmission. On the other hand, a four-pulse (repeated) train provokes the late phase of LTP (L-LTP, the protein-synthesis-dependent phase of LTP), lasting more than 4 h, and thus provides a model of strong synaptic stimulation (Huang and Kandel 1994).

Numerous E-LTP-related molecules (e.g., extracellular and transmembrane proteins, as well as their intracellular effectors) are found in the CA1 region of the hippocampus, where they might contribute to synaptic tagging-related signal transduction cascades. Data from mutant animals, especially knockout (KO) mice, indicate that these molecules participate in spatial learning and memory (Table 4.1).

Table 4.1 Mutant mice, E-LTP, spatial learning, and memory

Mutant[a]	E-LTP in CA1	Spatial learning/memory	Reference
CaMKII	Impaired	Impaired spatial learning	Hinds et al. (1998), Giese et al. (1998), Silva et al. (1992a, b)
Protein kinase C (PKC)-γ	Impaired	Impaired spatial learning	Abeliovich et al. (1993a, b)
Fyn	Impaired	Impaired spatial learning	Grant et al. (1992), Kojima et al. (1997)
Synaptic Ras GTPase-activating protein (SynGAP) (+/−)	Reduced	Impaired spatial learning	Komiyama et al. (2002)
Protein-tyrosine phosphatase (PTP)-δ	Enhanced	Impaired spatial learning	Uetani et al. (2000)
Neurogranin	Impaired	Impaired spatial learning	Huang et al. (2004)
LIM kinase 1	Enhanced	Impaired spatial learning	Meng et al. (2002)
Integrin α3	Impaired	Impaired spatial learning	Chan et al. (2007)
Integrin α8	Impaired	Spatial learning unaffected	Chan et al. (2010)
Integrin β1	Impaired	Impaired spatial learning and working memory	Chan et al. (2006), Huang et al. (2006b)
EphB2	Impaired	Impaired spatial learning	Henderson et al. (2001), Grunwald et al. (2001)
TrkB	Impaired	Impaired spatial learning	Minichiello et al. (1999)
Dopamine D1	Reduced	Impaired spatial learning	Granado et al. (2008)
Neural cell adhesion molecule (NCAM)	Impaired	Impaired fear memory	Muller et al. (2000), Senkov et al. (2006)
Tenascin-R	Impaired	Spatial learning unaffected	Saghatelyan et al. (2001)
Neuropsin	Impaired	Impaired spatial learning and working memory	Tamura et al. (2006)
BDNF	Reduced		Korte et al. (1995)

[a]Data are derived from KO animals unless otherwise noted

Moreover, the E-LTP-specific proteolysis of extracellular components by neuropsin, a neuronal serine protease, is a potential cellular/molecular mechanism involved in synaptic tagging (i.e., neuropsin-dependent synaptic tagging). This concept will be discussed in detail below.

4.2 E-LTP-Related Signaling Molecules That Are Modulated by Weak Stimulation

Signaling pathways responsible for the initial process of E-LTP and "gating" (the process whereby neuronal networks control input by inhibiting or promoting specific synaptic activity) from E-LTP into L-LTP still remain to be elucidated.

However, the induction of E-LTP after a single-tetanus stimulation in the CA1 region of the hippocampus is known to require Ca^{2+} influx through the *N*-methyl-D-aspartate (NMDA) receptor (Lisman 2003). Intracellular signaling begins with a slow (maximal 1–2-min) Ca^{2+}-dependent after depolarization, followed by activation of the NMDA receptor and elevation of postsynaptic cyclic AMP (cAMP) levels (Blitzer et al. 1995). Coincidentally, several cAMP-related molecules, such as cAMP-dependent protein kinase (PKA) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), participate in E-LTP induction.

In addition to their role in E-LTP induction, cAMP-activated PKA and CaMKII also block a protein phosphatase 1 (PP1)-operated inhibitory synaptic gating pathway. The gate is thereby maintained in the open state to execute synaptic responses for persistent plasticity (Blitzer et al. 1995; Otmakhova et al. 2000). The slow gating pathway is then closed by calcineurin to terminate LTP (Winder et al. 1998). CaMKII and PKA therefore control the gating mechanism from E-LTP into L-LTP by promoting synaptic modifications when Ca^{2+} levels increase (Okamoto et al. 2009). CaMKII is probably also involved in the setting of LTP-specific tags (Sajikumar et al. 2007; Redondo et al. 2010). Thus, E-LTP induction and synaptic tagging might share common and overlapping signal transduction mechanisms.

The role of PKA and CaMKII as "gate keepers" that alleviate the inhibitory constraint of PP1 and allow the transition from E-LTP into persistent plasticity/L-LTP was convincingly demonstrated by a number of studies employing hippocampal slices, electrophysiology techniques, and specific kinase inhibitors (Huang and Kandel 1994; Blitzer et al. 1995; Winder et al. 1998; Lisman 2003). The role of PKA in E-LTP/L-LTP was also explored in subsequent studies by using genetically engineered mice. For example, transgenic animals expressing a dominant negative form of the regulatory subunit of PKA showed a 50 % reduction in basal PKA activity, but continued to exhibit normal Schaffer-collateral E-LTP as induced by one- or two-pulse 100 Hz tetanic stimulation. However, L-LTP was clearly impaired (Abel et al. 1997). Thus, PKA is more likely to be necessary for L-LTP than for E-LTP itself. Nevertheless, conventional genetic approaches utilizing PKA regulatory subunit-KO animals failed to establish any decrease in PKA activity, or changes in Schaffer-collateral E-LTP and/or L-LTP (Brandon et al. 1995; Qi et al. 1996).

The G-protein-coupled dopamine D1/D5 and D4 receptors regulate postsynaptic cAMP and reportedly participate in the induction and regulation of E-LTP and L-LTP, respectively. The mesolimbic dopaminergic system projects from the ventral tegmental area to the limbic system via the nucleus accumbens, the amygdala, and the hippocampus, and is responsible for the relationship between memory acquisition and learning reinforcement (Lemon and Manahan-Vaughan 2006). The effect of the D1/D5 receptor on LTP has long been controversial, because the experimental results fluctuate according to the agonist employed and the experimental conditions (Mockett et al. 2004). Nevertheless, pharmacological studies using dopamine agonists have generally indicated that dopamine positively regulates E-LTP as well as L-LTP via the D1/D5 receptor (Frey et al. 1993; Huang and Kandel 1995; Otmakhova and Lisman 1996). In addition, in the recent gene-engineering study, E-LTP and

L-LTP were both markedly impaired in the hippocampus of D1 receptor gene-KO mice (Granado et al. 2008). Because further impairment was not imparted by supplementation of a D1/D5 antagonist to D1 receptor-deleted hippocampal slices, the investigators argued that the D1 receptor rather than the D5 receptor is critical for both types of LTP.

On the other hand, the D4 receptor triggers downregulation of intracellular cAMP levels by inhibiting the adenylyl cyclase-mediated G-protein α subunit, Gi. Current studies suggest that the dampening effect of D4 on E-LTP might be essential to the cognitive process (Herwerth et al. 2011). Furthermore, D4 modulation apparently occurs through NMDA receptors containing NR2B subunits, because such modulation is ablated in the hippocampus of mice lacking NR2B, but remains unaltered in the hippocampus of mice lacking NR2A (Herwerth et al. 2011). Notably, D4 receptor agonists increase γ oscillations, a risk factor for schizophrenia, in a manner similar to that afforded by neuregulin 1 (NRG1) (Fisahn et al. 2009; Andersson et al. 2012).

NRG1 and dopamine signaling pathways potentially crosstalk in gamma-aminobutyric acid (GABA)ergic interneurons to regulate the frequency of γ oscillations. Recently, Tamura et al. (2012) showed that neuropsin cleaves mature NRG1 to remove its heparin-binding domain, releasing the active form of NRG1 from the mature glycoprotein (Tamura et al. 2012). ErbB4 signaling induced by neuropsin-dependent proteolytic processing and subsequent release of NRG1 then modulates E-LTP via regulation of GABAergic transmission in the hippocampus (Fig. 4.1). Collectively, the convergence of dopamine- and neuropsin/NRG1-mediated signaling regulates intracellular cAMP levels in GABAergic neurons to control E-LTP.

In addition, certain neuromodulatory receptor signaling systems contribute to the regulation of E-LTP. Although only limited studies are available to date, some of these are briefly discussed below. For instance, the integrins comprise an important family of transmembrane cell adhesion receptors that function as heterodimers of α- and β-subunits. Integrins mediate diverse signaling processes in numerous cell populations, including neurons. Currently, 19 different α-subunits and eight different β-subunits are known in vertebrates, and over 20 different α/β heterodimers have been described. Mice with reduced expression of α3, α5, and α8 integrin subunits are defective in E-LTP (Chan et al. 2003, 2007), substantiating the involvement of the integrins in learning and memory. Furthermore, the integrin peptide antagonist, GRGDSP, as well as an infusion of function-blocking antibodies against the β1 integrin subunit, suppressed E-LTP and stabilize LTP in hippocampal slices (Stäubli et al. 1998; Kramár et al. 2006). Although the contribution of α5-containing integrins to LTP modulation has yet to be confirmed by a conditional genetic technology approach, conditional deletion of the β1 integrin subunit at a later postnatal stage compromised L-LTP induced by a two-tetanus protocol (Huang et al. 2006b). Further studies to reveal possible interactions between integrin signaling and LTP are necessary to clarify the precise role of these receptors.

Ephrin type-B receptor 2 (EphB2) interacts with and controls NMDA receptor activity, and as a result, EphB2 can modulate synaptic plasticity. EphB2 interacts

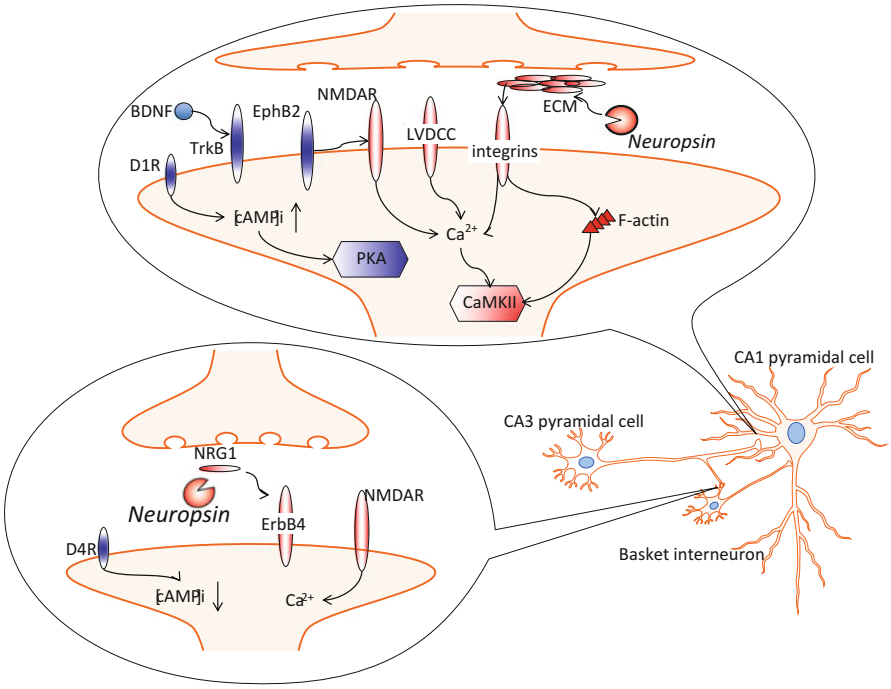

Fig. 4.1 E-LTP-induced signaling cascades are activated postsynaptically. Neuropsin modulates E-LTP and synaptic tagging via proteolysis-dependent postsynaptic signaling pathways. Neuropsin-dependent pathways are shown (*red*), one that involves integrin/CaMKII signaling, and another that involves NRG1/ErbB4 signaling

via its extracellular domain with the NR1, NR2A, and NR2B subunits of the NMDA receptor (Dalva et al. 2000). This interaction does not appear to be a simple two molecular interaction, but rather, a more complex heterogeneous interaction. In fact, activation of EphB2 results in clustering of NMDA receptors with other synaptic proteins, including αCaMKII (Dalva et al. 2000). EphB2 activation also enhances Ca^{2+} influx through the NMDA receptor, and is itself dependent on the phosphorylation of specific tyrosines in the NR2B subunit (Takasu et al. 2002). In addition, EphB2 deletion leads to deficits in synaptic plasticity (Grunwald et al. 2001; Henderson et al. 2001).

Investigations involving brain regions other than the hippocampus suggest that the molecular interaction between EphB2 and the NMDA receptor is, like the activation of NRG1, regulated by neuropsin-dependent proteolytic processing. In the amygdaloid complex, neuropsin cleaves EphB2 in response to stress. EphB2 regulates stress-induced plasticity and anxiety-like behavior, and its cleavage stimulates a dynamic interaction between the EphB2 and NMDA receptors, leading to an increase in the expression of an anxiety-related gene, FKBP5 (Attwood et al. 2011). The neuropsin/EphB2/NMDA receptor interaction is fast and specific for E-LTP, as evidenced by its disruption in the lateral-basal pathway of neuropsin-KO mice in

response to a weak stimulation protocol. The dynamic neuropsin/EphB2/NMDA receptor interaction ultimately results in increased NMDA receptor activity and manifestation of the behavioral signatures of anxiety.

Brain-derived neurotrophic factor (BDNF) causes synaptic plasticity in the fully developed brain, as well as in the immature brain. BDNF is produced by post-translational cleavage of a precursor protein termed proBDNF (Seidah et al. 1996; Pang et al. 2004; Matsumoto et al. 2008). BDNF is apparently involved in the regulation of E-LTP, because deletion of *Bdnf* in mice disrupted the induction of E-LTP in the CA1 region of hippocampal slices (Korte et al. 1995). The defect was rescued by reintroducing BDNF via viral transduction or by supplying exogenous BDNF (Korte et al. 1996; Patterson et al. 1996; Pozzo-Miller et al. 1999). Therefore, BDNF might be associated with the initiation of E-LTP.

Furthermore, pharmacological studies have demonstrated that the maintenance of L-LTP was also significantly impaired in hippocampal slices pretreated with tropomyosin receptor kinase (Trk) B antiserum, indicating an involvement of BDNF/TrkB signaling in L-LTP (Kang et al. 1997; Korte et al. 1998). Conditional deletion of *Trkb* from forebrain principal neurons also provided evidence for the involvement of TrkB in both E- and L-LTP, as assessed in hippocampal slices (Minichiello et al. 1999, 2002; Xu et al. 2000). The BDNF/TrkB system is controlled by Ca^{2+} influx through NMDA receptors and Ca^{2+} channels, enhancing TrkB receptor tyrosine kinase activity and facilitating ligand-induced internalization of TrkB (Du et al. 2003). In addition, cAMP expedites sorting of TrkB into the post-synaptic density (Ji et al. 2005). Because the BDNF/TrkB system participates in postsynaptic labeling by virtue of the molecular localization of TrkB, it may act as a tag-associated signaling system (Lu et al. 2011).

4.3 The Extracellular Protease Neuropsin Contributes to E-LTP

Neuropsin belongs to the family of secreted-type serine proteases, which are thought to be essential for many aspects of neuronal activity and function (Chen et al. 1995; Komai et al. 2000; Davies et al. 2001; Tamura et al. 2006; Ishikawa et al. 2008, 2011; Attwood et al. 2011). As described above, neuropsin stimulates GABAergic neurons via NRG1/ErbB4 signaling (Fig. 4.1). Recombinant neuropsin (produced by insect cells) modulates Schaffer-collateral E-LTP in a dose-dependent manner in hippocampal slices, and neuropsin enzyme activity (measured with synthetic neuropsin substrates) is transiently activated in the hippocampus during in vivo E-LTP in an NMDA receptor-dependent manner (Komai et al. 2000; Tamura et al. 2006; Ishikawa et al. 2008). Furthermore, electrophysiology investigations employing an E-LTP-preferential protocol (i.e., weak stimulation) showed that E-LTP is almost completely eradicated in hippocampal slices derived from neuropsin-KO mice. Consistent with this result, bath-application of a neuropsin-specific inhibitor to hippocampal slices derived from wild-type mice confirmed the E-LTP-specific

involvement of neuropsin in the CA1 region of the hippocampus (Hirata et al. 2001; Tamura et al. 2006; Ishikawa et al. 2008).

Interestingly, enzymatic activation of neuropsin is rather slow (requiring at least a few minutes) after a single tetanus-triggering protocol. The slow response of neuropsin may represent a sequential up-regulation of the enzyme after Ca^{2+}-dependent afterdepolarization (Blitzer et al. 1995; Tamura et al. 2006). Notably, neuropsin activation was abolished by a pharmacological NMDA receptor inhibitor. Behavioral studies showed that neuropsin protease deficiency caused a significant impairment of working memory-like behavior in the Y maze, as well as during the early stage of training in the Morris water maze (Tamura et al. 2006). Thus, the regulatory activity of neuropsin in the hippocampus (and likely in the amygdaloid complex as well; see above) was temporally restricted in E-LTP, rather than in L-LTP.

4.4 Neuropsin-Dependent and Independent Synaptic Tagging

Due to the distinctive feature of neuropsin's function in E-LTP alone, we postulated that the protease might contribute to an initial, protein synthesis-independent step in synaptic tag production. According to the original synaptic tagging hypothesis set forth by Frey and Morris (1997), two independent [weak (S1) vs. strong (S0)] synaptic inputs to the same neuronal population can be monitored by using a single recording electrode in the CA1 stratum radiatum. When the S0-mediated pathway is initiated by a strong stimulus, subsequent synaptic persistency is evoked in the S1-mediated pathway by a weak (single-tetanus) stimulus, which normally produces only E-LTP. This process represents the association of the strong and weak synaptic pathways.

However, our work showed that the S0/S1 association completely disappeared in hippocampal slices derived from neuropsin-KO mice, but recovered to normal levels by bath-application of an enzymatically active form of recombinant neuropsin. This observation suggests that neuropsin does indeed participate in an early step in synaptic tagging, as well as in the acquisition of persistency at the S1 site, where the single tetanus was delivered. We hypothesize that this neuropsin-dependent step encompasses the capture of PRP, as opposed to their synthesis. Additionally, a second form of synaptic association was evoked by a stronger (two-tetanus) stimulus at the S1 synapse, which perseveres in the neuropsin-KO mouse. Taken together, our findings support the existence of at least two types of synaptic association: neuropsin-dependent and neuropsin-independent synaptic association (Ishikawa et al. 2008).

Ample experimental evidence indicates that the neuropsin-dependent form of synaptic association is concomitantly driven by integrin/actin signaling and an L-type voltage-dependent Ca^{2+} channel (LVDCC)-mediated pathway (Ishikawa et al. 2008). For example, blockade of integrin function by the GRGDSP peptide, by an antibody against the β1 integrin subunit, by the actin polymerization inhibitor

cytochalasin D or by the LVDCC inhibitor nitrendipine all impaired neuropsin-dependent synaptic association (Fig. 4.1). The integrin-, the actin polymerization- and LVDCC-mediated signaling pathways probably converge into one or more common Ca^{2+}-dependent signaling pathways downstream of neuropsin, such as the CaMKII-dependent and/or the cAMP-dependent pathway. In support of this idea, KN93, a CaMKII inhibitor, was bath-applied to a recombinant neuropsin-supplemented (rescued) neuropsin-KO hippocampal slice. KN93, together with weak stimulation at S1, completely blocked the late associativity elicited at S1 in the stratum radiatum by a strong stimulation at S0 (Ishikawa et al. 2011). However, no study to date has directly examined whether neuropsin alters any molecular component(s) of the CaMKII-dependent or the cAMP-dependent signaling pathway to influence synaptic tagging. As such, further investigation is required to elucidate the detailed biochemical mechanism underlying neuropsin-dependent synaptic association.

Complicating matters further, the neuropsin-independent form of synaptic association may also involve LVDCC. A two- or more-tetanus stimulus induces NMDA-independent and LVDCC-dependent L-LTP and the formation of longer-lasting memories, particularly those based on stress-driven memory tasks (Grover and Teyler 1990; Cavuş and Teyler 1996) (e.g., food exploration in the radial maze under conditions of severe starvation (Borroni et al. 2000), and fear conditioning (Moosmang et al. 2005; McKinney and Murphy 2006). Thus, neuropsin (integrin/actin signaling)-dependent and neuropsin-independent late associativity apparently come together into the same LVDCC-mediated intracellular signaling pathway (Ishikawa et al. 2008).

4.5 Conclusions

Recent studies have revealed several novel potential mechanisms of synaptic tagging in which integrin, neuropsin, dopamine receptors, PKA, protein kinase Mzeta (PKMz), TrkB, and CaMKII all participate in local and synapse-specific regulation of E-LTP signaling and E-LTP transition into L-LTP (Sajikumar et al. 2007; Ishikawa et al. 2008, 2011; Redondo et al. 2010; Attwood et al. 2011; Lu et al. 2011; Tamura et al. 2012). These signaling molecules are probably shared among common and overlapping E-LTP and synaptic tagging pathways.

The mechanisms underlying synaptic tagging are triggered by Ca^{2+} influx through synaptic NMDA receptors and other Ca^{2+} channels, followed by an enhancement in cAMP- and CaMKII-dependent signaling at local synapses. A series of studies from our group revealed the existence of neuropsin-dependent and -independent forms of synaptic tagging in the hippocampus. Other investigations demonstrated that CaMKII may function as a component of a "gating" mechanism for the acquisition of persistency from E-LTP into L-LTP by promoting cAMP-dependent protein modifications (Okamoto et al. 2009) and by situating LTP-specific tags at appropriate sites (Sajikumar et al. 2007; Redondo et al. 2010). Thus, the outside-in signaling

associated with synaptic gating may utilize several independent intracellular pathways that converge into a single CaMKII-mediated regulatory mechanism for setting the tag at a specific synapse. As described above, LVDCC-mediated signaling possibly also supports the acquisition of synaptic persistency.

Neural activity-dependent proteolytic processing of neuropsin substrates (e.g., NRG1 and various extracellular matrix molecules) results in the exertion of multiple signals toward the acquisition of synaptic plasticity, thus contributing to changes in synaptic configurations. Neuropsin-dependent synaptic tagging via outside-in signaling, as mediated through NRG1/ErbB4 and integrins/CaMKII (Fig. 4.1), might place some as yet unidentified mark on Schaffer-collaterals and interneuronal synapses related to the procurement of late associativity (Ishikawa et al. 2008, 2011; Tamura et al. 2012). Although neuropsin is apparently crucial for this process, direct mechanisms for the attainment of synaptic persistency are still unknown. One possibility is that a CaMKII-dependent modulation of F-actin induces delivery to and capture of PRPs within a specific tagged dendritic spine (Okamoto et al. 2009).

In addition, theoretical work suggests that theta rhythms might act as a type of "tag" for short-term memory processing in the hippocampus (Vertes 2005). Theta rhythms selectively appear in the rodent during periods of active exploratory movement. If the exploratory information is temporally coupled to theta rhythms, the theta rhythm-induced storage mechanism of novel information in the hippocampus may be similar to that of synaptic tagging-induced initiation of E-LTP.

Although molecular and cellular cognition studies have provided compelling evidence that synaptic plasticity and synaptic associativity are required for learning and memory, it is still unclear where and how they act in the brain. The field is full of major questions, including the nature of the molecular and cellular mechanisms of plasticity and memory that encode, edit, and use stored information. Certainly, a more complete understanding of the fundamental signaling pathways responsible for LTP and synaptic tagging will continue to further our understanding of the identity and functioning of the neuronal networks behind learning and memory.

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