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BDNF: A Key Regulator for Protein-synthesis Dependent LTP and Long-term Memory?

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Abstract

It is generally believed that late-phase long-term potentiation (L-LTP) and long-term memory (LTM) require new protein synthesis. Although the full complement of proteins mediating the long-lasting changes in synaptic efficacy have yet to be identified, several lines of evidence point to a crucial role for activity-induced brain derived neurotrophic factor (BDNF) expression in generating sustained structural and functional changes at hippocampal synapses thought to underlie some forms of LTM. In particular, BDNF is sufficient to induce the transformation of early to late phase LTP in the presence of protein synthesis inhibitors, and inhibition of BDNF signaling impairs LTM. Despite solid evidence for a critical role of BDNF in L-LTP and LTM, many issues are not resolved. Given that BDNF needs to be processed in Golgi outposts localized at the branch point of one or few dendrites, a conceptually challenging problem is how locally synthesized BDNF in dendrites could ensure synapse-specific modulation of L-LTP. An interesting alternative is that BDNF-TrkB signaling is involved in synaptic tagging, a prominent hypothesis that explains how soma-derived protein could selectively modulate the tetanized (tagged) synapse. Finally, specific roles of BDNF in the acquisition, retention or extinction of LTM remain to be established.

Keywords

synaptic plasticity; TrkB; presynaptic; postsynaptic; local translation; dendritic; tetanic stimulation; synaptic tagging; encoding; consolidation; extinction

Introduction

Synaptic plasticity describes the process by which connections between two neurons, or synapses, change in strength. By definition, it is a functional term referring to an increase or decrease in synaptic efficacy, but we now know that the physiological changes in the strength of transmission are often accompanied by structural alterations of the synapses. Since memories are believed to be stored in synapses of the brain, synaptic plasticity is thought to be the cellular mechanism for learning and memory. LTP in the hippocampus is the most

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studied form of synaptic plasticity. It has been widely accepted that LTP can be divided into at least two temporally distinct phases that are fundamentally different in their underlying mechanisms. A weak, high frequency tetanus (e.g. a train of 100 pulses at 100 Hz) can trigger an increase in synaptic efficacy that lasts for 1-2 hours. This short-lasting form of LTP is called early phase LTP (E-LTP). E-LTP requires modification of existing proteins and their trafficking at synapses but not de novo protein synthesis (Bliss and Collingridge, 1993; Malenka and Bear, 2004). On the other hand, repeated, strong high frequency stimulations (e.g. multiple trains of 100 pulses at 100 Hz) can induce an increase in synaptic efficacy lasting over 8 hours (Frey, Krug, Reymann, and Matthies, 1988) or even days (Abraham, 2003). L-LTP differs from E-LTP in its requirement for de novo mRNA and in its association with structural changes at synapses (Frey et al., 1988; Harris, Fiala, and Ostroff, 2003; Kandel, 2001; Krug, Lossner, and Ott, 1984; Muller, Nikonenko, Jourdain, and Alberi, 2002; Yuste and Bonhoeffer, 2001). It is generally believed that the E-LTP and L-LTP inducing stimuli trigger very different, albeit partially overlapping, biochemical pathways that lead to distinct changes at synapses. In particular, induction of L-LTP results in activation of cAMP-dependent protein kinase (PKA) and mitogen-associated protein kinase (MAPK, also known as extracellular signal-related protein kinase, ERK) (Kandel, 2001; Pang and Lu, 2004). Subsequently, several constitutively expressed transcription factors (e.g. cAPM/calcium responsive-element binding protein (CREB), and Elk-1) are phosphorylated and activated for the transcription of downstream genes that presumably mediate the changes in the structure and/or function of the synapses (Kandel, 2001; Shaywitz and Greenberg, 1999). One of the downstream genes induced by the L-LTP-inducing tetanus is BDNF.

BDNF is a small dimeric protein that works through high affinity binding with the receptor tyrosine kinase, tropomyosin-related kinase B (TrkB). BDNF and TrkB are widely distributed across subregions of the hippocampus and the adult forebrain (Bramham and Messaoudi, 2005). BDNF containing secretory vesicles are present in both axon terminals (presynaptic site) and dendrites (postsynaptic site) of glutamatergic principal neurons (granule cells and pyramidal cells) (Fawcett, Aloyz, McLean, Pareek, Miller, McPherson, and Murphy, 1997; Haubensak, Narz, Heumann, and Lessmann, 1998; Kohara, Kitamura, Morishima, and Tsumoto, 2001; Kojima, Takei, Numakawa, Ishikawa, Suzuki, Matsumoto, Katoh-Semba, Nawa, and Hatanaka, 2001; Lessmann, Gottmann, and Malcangio, 2003; Lu, 2003). BDNF stands out among all neurotrophins in the activity-dependent regulation of its expression and secretion. Upon high frequency stimulation, BDNF is secreted in a manner dependent on Ca^{2+} influx through NMDA subtype glutamate receptors or voltage-gated Ca^{2+} channels (Aicardi, Argilli, Cappello, Santi, Riccio, Thoenen, and Canossa, 2004; Balkowiec and Katz, 2002; Gartner and Staiger, 2002; Hartmann, Heumann, and Lessmann, 2001; Lever, Bradbury, Cunningham, Adelson, Jones, McMahon, Marvizon, and Malcangio, 2001). BDNF can also be secreted from either postsynaptic spines or presynaptic terminals. Possible mechanisms to trigger secretion include activation of N-type Ca^{2+} channels and mobilization of Ca^{2+} from intracellular stores (Balkowiec and Katz, 2002). Once secreted into the synaptic cleft, BDNF can bind to TrkB localized at both pre- and postsynaptic sites of glutamatergic synapses (Drake, Milner, and Patterson, 1999). In the postsynaptic density (PSD), TrkB is associated with PSD95 and NMDA receptors (Aoki, Wu, Elste, Len, Lin, McAuliffe, and Black, 2000; Husi, Ward, Choudhary, Blackstock, and Grant, 2000; Ji, Pang, Feng, and Lu, 2005; Yoshii and Constantine-Paton, 2007). In addition, the expression of BDNF, particularly transcription of the BDNF gene through promoter III, is tightly controlled by neuronal activity (Chen, Chang, Lin, Meissner, West, Griffith, Jaenisch, and Greenberg, 2003).

Given the synaptic localization of TrkB and activity-dependent secretion of BDNF protein and transcription of BDNF mRNA, it is not surprising that BDNF has emerged as a key regulator of synaptic plasticity and memory (Lu, 2003;Pang and Lu, 2004;Poo, 2001). Significant progress has been made in understanding the role of BDNF in E-LTP and short-term memory.

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BDNF facilitates the induction of E-LTP by enhancing synaptic responses to tetanus stimulation (Figurov, Pozzo-Miller, Olafsson, Wang, and Lu, 1996;Gottschalk, Pozzo-Miller, Figurov, and Lu, 1998;Rex, Lauterborn, Lin, Kramar, Rogers, Gall, and Lynch, 2006;Yano, Ninan, Zhang, Milner, Arancio, and Chao, 2006). This is most likely due to BDNF regulation of synaptic vesicle mobilization and docking, possibly by regulating the distribution and phosphorylation of synaptic proteins (Pozzo-Miller, Gottschalk, Zhang, McDermott, Du, Gopalakrishnan, Oho, Sheng, and Lu, 1999), (Jovanovic, Czernik, Fienberg, Greengard, and Sihra, 2000). BDNF also plays a role in the maintenance (or expression) of E-LTP, possibly by activating “silent synapses” (Shen, Wu, Zhang, Dou, Rao, Chen, and Duan, 2006) and/or by regulating actin motor complex (Rex, Lin, Kramar, Chen, Gall, and Lynch, 2007;Yano et al., 2006). Moreover, studies of the well-known val66met polymorphism in the human BDNF gene (Egan, Kojima, Callicott, Goldberg, Kolachana, Bertolino, Zaitsev, Gold, Goldman, Dean, Lu, and Weinberger, 2003) suggest that activity-dependent secretion of BDNF is critical for short-term, hippocampal dependent episodic memory that is largely dependent on E-LTP. In contrast, progress on the studies of BDNF in L-LTP and LTM is lagging behind. Nevertheless, numerous reports have demonstrated that BDNF is critical for the induction and maintenance of L-LTP. This review will focus on our current knowledge with respect to action sites, sufficiency, and expression of BDNF in hippocampal L-LTP and LTM.

Role of BDNF in hippocampal L-LTP

Is activity-dependent expression of endogenous BDNF sufficient to mediate L-LTP?

A variety of genetic and pharmacological studies suggest that BDNF is necessary for L-LTP to occur. In heterozygous BDNF (+/-) knockout mice, there is a significant deficit in L-LTP induced by several different protocols including theta burst stimulation or forskolin application (Korte, Carroll, Wolf, Brem, Thoenen, and Bonhoeffer, 1995; Pang, Teng, Zaitsev, Woo, Sakata, Zhen, Teng, Yung, Hempstead, and Lu, 2004; Patterson, Pittenger, Morozov, Martin, Scanlin, Drake, and Kandel, 2001). Treatment of hippocampal slices by the BDNF scavenger TrkB-Fc or antibodies against BDNF or TrkB also inhibits L-LTP (Kang, Welcher, Shelton, and Schuman, 1997). Similarly, L-LTP is impaired in TrkB knockout mice (Minichiello, Korte, Wolfer, Kuhn, Unsicker, Cestari, Rossi-Arnaud, Lipp, Bonhoeffer, and Klein, 1999), as well as in mice with a targeted mutation in the phospholipase C-γ (PLC-γ) docking site (but not in the Shc site) on TrkB (Minichiello, Calella, Medina, Bonhoeffer, Klein, and Korte, 2002). Curiously, the classic L-LTP induced by multiple tetani is normal in BDNF+/- mice, suggesting that BDNF is not involved in all forms of long-term synaptic plasticity (Chen, Kolbeck, Barde, Bonhoeffer, and Kossel, 1999; Kang et al., 1997; Patterson et al., 2001).

While these findings suggest that endogenous BDNF is required for the maintenance of L-LTP, a critical question is whether an activity-dependent increase in endogenous BDNF is responsible for the maintenance of L-LTP. Converging experimental results strongly suggest that this is the case. First, BDNF transcription is enhanced by L-LTP-inducing stimuli. With in situ hybridization, BDNF mRNA level is found to increase in the hippocampal CA1 region and dentate gyrus within 2-4 hours after the application of L-LTP-inducing tetanic stimulation (Castren, Pitkanen, Sirvio, Parsadanian, Lindholm, Thoenen, and Riekkinen, 1993; Dragunow, Beilharz, Mason, Lawlor, Abraham, and Gluckman, 1993; Patterson, Grover, Schwartzkroin, and Bothwell, 1992). Thus, the level of BDNF is increased either as a cause or as a result of L-LTP induction. Second, the impairment of L-LTP observed in BDNF+/- mice could be rescued by a perfusion of exogenous BDNF (Korte, Griesbeck, Gravel, Carroll, Staiger, Thoenen, and Bonhoeffer, 1996; Pang et al., 2004), indicating that an increase in BDNF may contribute to the maintenance of L-LTP. Moreover, recent studies from this group found that in a line of mutant mice in which the activity-dependent surge of BDNF mRNA is blocked, L-LTP is selectively disrupted whereas E-LTP is intact (Sakata, Woo, Wu, Shen, and Lu, 2005). These results suggest that without an increase in BDNF levels a strong tetanus is not

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sufficient to induce L-LTP. Finally, when protein synthesis was completely inhibited by either anisomycin or emitin, L-LTP was blocked in the hippocampus (Frey and Morris, 1997; Scharf, Woo, Lattal, Young, Nguyen, and Abel, 2002). Remarkably, application of exogenous BDNF rescued the L-LTP deficit even when all new protein synthesis is blocked (Pang et al., 2004). Thus, BDNF may be the key (if not the only) protein synthesis product responsible for the long-term maintenance of L-LTP. Taken together, these results support a model in which L-LTP-inducing stimuli increase endogenous BDNF and this increase may support the expression of L-LTP.

Despite its critical role in L-LTP, BDNF by itself is incapable of inducing synaptic potentiation. Earlier reports show that a brief bath application of BDNF for several minutes can trigger a sustained potentiation of synaptic efficacy at CA1 synapses in hippocampal slices (Kang and Schuman, 1995; 1996). Numerous laboratories have attempted to replicate this finding but failed (Figurov et al., 1996; Frerking, Malenka, and Nicoll, 1998; Gottschalk et al., 1998; Huber, Sawtell, and Bear, 1998; Kramar, Lin, Lin, Arai, Gall, and Lynch, 2004; Patterson, Abel, Deuel, Martin, Rose, and Kandel, 1996; Tanaka, Saito, and Matsuki, 1997). The rapid, direct enhancement of synaptic efficacy was later attributed to an unusually high speed of BDNF perfusion (Kang, Jia, Suh, Tang, and Schuman, 1996), the physiological significance of which remains unclear. BDNF-induced LTP was subsequently reported in the medial perforant path-granule cell synapses in the hippcampal dentate (Messaoudi, Bardsen, Srebro, and Bramham, 1998; Messaoudi, Ying, Kanhema, Croll, and Bramham, 2002; Ying, Futter, Rosenblum, Webber, Hunt, Bliss, and Bramham, 2002). In these studies, infusion of BDNF to the dentate was found to elicit a continuous increase in EPSPs over a long period of time (24 hours) (Bramham and Messaoudi, 2005). So far, there is no published report from other laboratories that supports or disputes such results. This appears to be an unusual form of plasticity whose relevance to learning and memory remains to be investigated. Since there is no need for synaptic stimulation, this form of plasticity is clearly activity-independent, making it difficult to conform with the conceptual framework of learning and memory. A surge of BDNF concentration pharmacologically may force synapses to behave out of their physiological norm. Finally, it is difficult to ensure synapse-specificity, a fundamental property of LTP, if BDNF undiscriminatorily potentiates all synapses.

Does L-LTP require pre- or postsynaptic synthesis of BDNF?

There is no dispute that L-LTP requires a sustained increase in endogenous BDNF for its long-lasting maintenance. An interesting and yet unresolved issue is whether the endogenous BDNF is derived pre- or postsynaptically. Early work suggests that E-LTP at the Schaffer collateral-CA1 synapses requires BDNF derived from presynaptic CA3 neurons, but not postsynaptic CA1 neurons (Zakharenko, Patterson, Dragatsis, Zeitlin, Siegelbaum, Kandel, and Morozov, 2003). The initial surge of BDNF may be due to the secretion of preexisting BDNF-containing vesicles from presynaptic terminals of CA3 neurons, induced by high frequency stimulation (HFS). This may be important for the induction of E-LTP. Due to the low expression level of BDNF in neurons, however, the existing BDNF would eventually be exhausted. Thus, for the long-term maintenance of L-LTP, a sustained supply of BDNF may come primarily from new protein synthesis triggered by repeated strong synaptic stimulation. This idea is supported by the findings that BDNF mRNA levels in the hippocampus are significantly increased 1-3 hours after the L-LTP-inducing tetanic stimulation (Castren et al., 1993; Dragunow et al., 1993; Morimoto, Sato, Sato, Yamada, and Hayabara, 1998; Patterson et al., 1992). Moreover, the slow kinetics of BDNF transcription may also serve as a potential mechanism that translates acute high-frequency synaptic activity to long-lasting alteration of synaptic physiology and morphology (Lu, 2003).

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At CA1 synapses, does newly synthesized BDNF come from pre- or postsynaptic neurons? When the Schaffer-collateral pathway is stimulated with HFS, an increase in BDNF mRNA was only observed in postsynaptic CA1, but not in presynaptic CA3, neurons (Patterson et al., 1992). This finding indicates that L-LTP requires postsynaptic BDNF mRNA synthesis. In addition, the activity-dependent up-regulation of postsynaptic BDNF gene expression requires an increase in intracellular Ca^{2+} concentration through NMDA receptors or L-type Ca^{2+} channels activated during HFS (Ghosh, Carnahan, and Greenberg, 1994; Sano, Nanba, Tabuchi, Tsuchiya, and Tsuda, 1996; Shieh, Hu, Bobb, Timmusk, and Ghosh, 1998; Tabuchi, Nakaoka, Amano, Yukimine, Andoh, Kuraishi, and Tsuda, 2000; Tao, Finkbeiner, Arnold, Shaywitz, and Greenberg, 1998; Zafra, Lindholm, Castren, Hartikka, and Thoenen, 1992). This is inconsistent with a presynaptic Ca^{2+} influx, since it is restricted to presynaptic terminals and is mediated primarily through N- or P/Q type Ca^{2+} channels. Moreover, pairing of a weak presynaptic tetanus with repetitive somatic action potentials in CA1 neurons was sufficient to induce transcription of genes, including BDNF, as well as L-LTP (Dudek & Fields, 2002; Lee, Cohen, Becker & Fields, 2005). Taken together, the existing data support the notion that while activity-dependent secretion of BDNF from presynaptic sites may be necessary for E-LTP, the long-term maintenance of L-LTP requires sustained supply of BDNF through activity-dependent transcription and translation in the postsynaptic neurons (Fig. 1).

Does local synthesis of BDNF at dendrites play a role in L-LTP?

Another important issue is how BDNF, a diffusible factor, achieves synapse-specific modulation during L-LTP? A potential mechanism is activity-dependent translation of BDNF mRNA locally at synapses undergoing L-LTP. Thus, a strong tetanus (but not a weak tetanus) should stimulate the synthesis, processing and secretion BDNF protein right at the tetanized synapses, using BDNF mRNA localized in that dendritic branch. While conceptually attractive, there is, at best, limited evidence supporting this model. In fact, the functional role of dendritic protein synthesis at large remain obscure, despite the fact that numerous experiments have demonstrated local translation of proteins (particularly the cytosolic proteins) and its activity-dependence, in neuronal dendrites (Grossman, Aldridge, Weiler, and Greenough, 2006; Martin, 2004; Sutton and Schuman, 2006). In particular, the function of local dendritic translation in L-LTP has been demonstrated only partially for one protein: CaMKIIα. In a mouse mutant in which the native 3′UTR of CaMKIIα mRNA was replaced with the 3′UTR of bovine growth hormone (Miller, Yasuda, Coats, Jones, Martone, and Mayford, 2002), the translation of CaMKIIα protein is intact, but the dendritic localization of CaMKIIα mRNA is impaired. This is accompanied by deficits in L-LTP and hippocampal-dependent long-term memory, but not E-LTP (Miller et al., 2002). There is no evidence for a role of dendritic BDNF synthesis in L-LTP so far.

If local BDNF synthesis does play a critical role in L-LTP then there must be dendritic localization of BDNF mRNA. Indeed, several early studies have reported the localization of BDNF mRNA in the dendrites of cultured hippocampal pyramidal neurons (Crino and Eberwine, 1996; Tongiorgi, Righi, and Cattaneo, 1997). Subsequent studies showed that neuronal activity enhances the dendritic trafficking of BDNF mRNA both in cultured hippocampal neurons and in CA1 neurons in vivo (Simonato, Bregola, Armellin, Del Piccolo, Rodi, Zucchini, and Tongiorgi, 2002; Tongiorgi et al., 1997), that accumulation of BDNF mRNA in distal dendrites requires Ca2+ influx through NMDA receptor and L-type Ca2+ channels and the activation of PI3 kinase pathway (Righi, Tongiorgi, and Cattaneo, 2000; Tongiorgi et al., 1997), and that exon-IV mRNA is the primary BDNF mRNA translocated to dendrites (Pattabiraman, Tropea, Chiaruttini, Tongiorgi, Cattaneo, and Domenici, 2005). Since BDNF itself can induce dendritic targeting of BDNF mRNA, it is possible that tetanus-induced secretion of BDNF may serve as a signal for the localization of BDNF mRNA to these activated synapses (Righi et al., 2000).

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Dendritic BDNF mRNA appears to be associated with polyribosomes, suggesting active translation (Tongiorgi, Armellin, Giulianini, Bregola, Zucchini, Paradiso, Steward, Cattaneo, and Simonato, 2004). Consistent with this, BDNF immuno-reactivity in dendrites was rapidly increased upon neuronal depolarization or seizure (Tongiorgi et al., 2004; Tongiorgi et al., 1997). Moreover, the increase in BDNF immuno-reactivity was blocked by the protein synthesis inhibitor cycloheximide, but not the inhibitor for dendritic transporter nocodazole (Tongiorgi et al., 1997). These results suggest an increase in local translation of BDNF in dendrites, rather than an increase in transport of BDNF protein from soma to dendrites. However, given that the BDNF antibody used in these experiments could detect signals in BDNF-/- mice, further work is necessary to confirm these results. Thus, despite the evidence for dendritic localization of BDNF mRNA, activity-dependent dendritic translation of BDNF protein remains to be firmly established.

A conceptually more challenging issue is how locally synthesized secretory or transmembrane proteins get processed. There are a number of post-translational modifications for BDNF, including glycosylation, proper folding, cleavage, and sorting to constitutive or regulated secretion pathway. Folding and N-glycosylation are processed in ER whereas cleavage and sorting occur in Golgi apparatus or subsequent organelles. In a provocative paper, Mike Ehlers and colleagues demonstrated that at least in cultured hippocampal neurons, Golgi apparatus are absent in majority of dendrites (Horton, Racz, Monson, Lin, Weinberg, and Ehlers, 2005). Using markers specific for Golgi, they show that small, Golgi-like organelles (so-called Golgi outposts) are selectively localized to dendritic branch points and are typically present in only one of the dendrites (Fig. 2). This study poses a number of important conceptual challenges to local synthesis of BDNF. First, most dendritically synthesized BDNF has to be transported back to the neuronal soma to be processed in Golgi apparatus. Second, even in the long (apical) dendrite, BDNF synthesized in distal dendrites still needs to be transported to the branch point to be sorted in the Golgi outposts. In both cases, a round-trip trafficking of BDNF is implicated, and synapse specificity is lost (Fig. 2). Third, assuming that locally translated BDNF could be secreted after glycosylation and correctly folded in ERs in the distal dendrites without Golgi, it would only be secreted in a constitutive manner in the form of proBDNF, because sorting to the regulated secretion pathway and intracellular cleavage can only happen in Golgi. The requirement of round-trip transport for BDNF processing makes it difficult to ensure a selective modulation of the stimulated synapse (A in Fig. 2) without affecting other synapses (B and C in Fig. 2).

Does BDNF serve as a plasticity-related protein in synaptic tagging?

In addition to de novo protein synthesis, maintenance of L-LTP, like that of LTM, also requires activity-dependent gene transcription, which occurs in the nucleus located in the cell body of neurons. Another fundamental question then is how the newly synthesized protein(s) are specifically targeted to, or “captured” by, the tetanized synapses without affecting nearby un-tetanized synapses. The synaptic “tagging” hypothesis is a prominent model that accounts for synapse-specificity of L-LTP (Frey and Morris, 1997). In this hypothesis, a strong tetanus induces protein synthesis in the soma, these “plasticity-related proteins (PRPs)” are then transported to dendrites. The PRPs can only be captured by the synaptic tags previously created by tetanic stimulation, leading to modification of only the tetanized (activated) synapses (Fig. 3C). A weak tetanus is sufficient to generate a tag, but the tag is generally short-lived. The best demonstration of synaptic tagging is the two-pathway experiment in which two independent synaptic inputs to the same neuronal population are activated by two stimulating electrodes, while field EPSPs are monitored by a single recording electrode in the Schaffer collateral region of the CA1 (Fig. 3A and 3B). When one afferent pathway (S1) to a specific population of CA1 neurons is activated by strong tetanus, a weak tetanus applied to a second independent pathway

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(S2) usually induces L-LTP because it creates a tag that captures the PRP induced by the strong tetanus in S1.

The nature and identity of the PRPs and synaptic tags remain to be established (Reymann and Frey, 2007). Several lines of evidence suggest that BDNF could serve as a PRP. First, substantial experimental data support the fact that strong tetani enhance the expression of BDNF as a PRP in the soma of CA1 pyramidal neurons (Castren et al., 1993; Dragunow et al., 1993; Patterson et al., 1992). This is possibly mediated by BDNF transcription through promoter III (Lee, Cohen, Becker, and Fields, 2005). Microarray experiments demonstrate that strong, L-LTP inducing stimulation results in an increase in the expression of 100 genes, but only three genes qualify statistically as L-LTP specific genes. Among the three, BDNF fits the best as a PRP (Barco, Patterson, Alarcon, Gromova, Mata-Roig, Morozov, and Kandel, 2005). Direct proof of the trafficking of newly synthesized BDNF and its capture at the tetanized synapse has yet to be reported. Second, coupling of weak tetanic stimulation, which creates a “synaptic tag” but not PRP expression, and elevated BDNF levels can induce L-LTP. It has been shown that pairing BDNF perfusion with a set of sub-threshold tetani could induce LTP which otherwise would not occur with stimulation alone (Figurov et al., 1996; Kovalchuk, Hanse, Kafitz, and Konnerth, 2002). Pang et al performed a similar experiment but examined L-LTP explicitly. They showed that a set of weak theta bursts (3 sets of TBS, or 3TBS), which normally could induce E-LTP but not L-LTP, elicited reliable L-LTP that lasts more than 3 hours when paired with a perfusion of BDNF (Pang et al., 2004). In VP16-CREB mice in which BDNF levels are elevated, a weak tetanus could induce L-LTP, which is reversed by TrkB-IgG (Barco et al., 2005). Third, when PRP production is completely blocked by protein synthesis inhibitors, strong tetani no longer induce L-LTP. Remarkably, application of exogenous mBDNF completely rescues the deficit in L-LTP (Pang et al., 2004). If the synaptic tag is short lived, then the newly generated PRP should only work within a finite time window after delivery of strong tetani. Indeed, application of TrkB-IgG, a BDNF scavenger, to hippocampal slices within 70 min after the tetanus can reverse an already established LTP (Kang et al., 1997). Finally, the capture of activity-induced BDNF by a weakly tetanized synapse has been demonstrated in the “two pathway” experiment (Barco et al., 2005). In wild type mice, a weak tetanus to the second pathway (S2) could induce L-LTP if it is preceded by a strong tetanus to the first pathway (S1) (Fig. 3B). In mice in which the BDNF gene is deleted in the hippocampus (or more specifically in postsynaptic CA1 neurons which could produce PRPs), a weak tetanus can no longer capture PRPs to sustain L-LTP in S2 (Barco et al., 2005).

If BDNF is a PRP, a natural question is whether TrkB, the receptor for BDNF, can serve as a synaptic tag. A synaptic tag has to satisfy several criteria (Kelleher, Govindarajan, and Tonegawa, 2004): 1) the tag can be activated by weak tetanus that induces only E-LTP; 2) the lifetime of the tag is about 1–2 hours; 3) the activation of the tag does not require protein synthesis; 4) the tag is induced in an input-specific and physically immobile manner; and 5) the tag interacts with PRP for L-LTP. A twist of the “tagging” model here is that the PRP (BDNF) needs to be secreted before it can be captured by the tag (TrkB). Demonstrating that TrkB is a “synaptic tag” represents the ultimate challenge in the hypothesis that BDNF-TrkB is a PRP-tag pair in synaptic tagging.

Role of BDNF in hippocampal-dependent long-term memory

As the putative cellular mechanism underlying memory formation, LTP has been correlated with the acquisition and retention of learned behaviors. Distinct forms of LTP, defined by unique temporal and molecular characteristics, mirror many temporal and mechanistic aspects of memory formation. Hippocampal-dependent memory can also be divided into at least two phases, short-term and long-term. Like E-LTP, short-term memory (STM) lasts from minutes

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to a few hours and does not require protein or mRNA synthesis. In contrast, long-term memory (LTM) lasts from many hours to days, weeks, or even longer. In addition, both LTM and L-LTP are dependent on mRNA and protein synthesis (Dudai, 2004; McGaugh, 2000). It is tempting to map early and late phase LTP onto these short and long-term forms of memory and indeed there is much evidence to support this delineation. Several downstream effectors of Ca^{2+} and cAMP-mediated signaling have been shown to regulate both L-LTP and LTM in a similar manner (Abel, Nguyen, Barad, Deuel, Kandel, and Bourtchouladze, 1997; Costa-Mattioli, Gobert, Stern, Gamache, Colina, Cuello, Sossin, Kaufman, Pelletier, Rosenblum, Krnjevic, Lacaille, Nader, and Sonenberg, 2007; Kang, Sun, Atkins, Soderling, Wilson, and Tonegawa, 2001). However, it is not clear to what extent the molecular mechanisms underlying LTP are applicable to different forms of memory – even when those memories depend on the same anatomical structure, such as the hippocampus. Furthermore, it is not certain whether induction and maintenance of L-LTP in the hours immediately following memory acquisition is itself sufficient to maintain memory weeks or months after initial learning. In order to fully understand how BDNF regulates LTM, it will be important to determine when BDNF-dependent L-LTP is required for successful memory acquisition, retention, or retrieval.

Formation (acquisition or encoding) of LTM

Despite the fact that L-LTP inducing stimuli or learning turns on (or off) the expression of a set of common genes in the hippocampal neurons involved, the specific genes that mediate specific aspects of LTM have not been fully established (Ingi, Worley, and Lanahan, 2001; Matsuo, Murayama, Saitoh, Sakaki, and Inokuchi, 2000; Qian, Gilbert, Colicos, Kandel, and Kuhl, 1993). Nevertheless, evidence seems quite strong that BDNF is critically involved in LTM. An increase in BDNF mRNA in the hippocampus has been observed following acquisition of spatial tasks such as the Morris water maze and the radial maze (Kesslak, So, Choi, Cotman, and Gomez-Pinilla, 1998; Mizuno, Yamada, Olariu, Nawa, and Nabeshima, 2000); aversive conditioning in the form of inhibitory avoidance (Alonso, Vianna, Depino, Mello e Souza, Pereira, Szapiro, Viola, Pitossi, Izquierdo, and Medina, 2002; Ma, Wang, Wu, Wei, and Lee, 1998), contextual fear conditioning (Hall, Thomas, and Everitt, 2000); and olfactory recognition (Broad, Mimmack, Keverne, and Kendrick, 2002). In parallel, blocking BDNF synthesis or TrkB availability has been shown to impair LTM formation: BDNF+/- mice are impaired in Morris water maze acquisition (Linnarsson, Bjorklund, and Ernfors, 1997) and contextual fear conditioning (Liu, Lyons, Mamounas, and Thompson, 2004); deletion of the TrkB gene in the forebrain results in severe behavioral deficits in a spatial water maze task and moderate deficits in a radial arm maze task (Minichiello et al., 1999); inhibition of BDNF mRNA expression via hippocampal infusion of BDNF antisense oligos or anti-BDNF antibody before training blocks acquisition in inhibitory avoidance and radial arm maze tasks (Alonso et al., 2002; Ma et al., 1998; Mizuno et al., 2000). Genetic and pharmacological manipulations of BDNF signaling prior to training have also been shown to impair LTM (Gorski, Balogh, Wehner, and Jones, 2003; Heldt, Stanek, Chhatwal, and Ressler, 2007; Johnston, Clements, and Rose, 1999; Koponen, Voikar, Riekki, Saarelainen, Rauramaa, Rauvala, Taira, and Castren, 2004; Monteggia, Barrot, Powell, Berton, Galanis, Gemelli, Meuth, Nagy, Greene, and Nestler, 2004; Mu, Li, Yao, and Zhou, 1999; Saarelainen, Pussinen, Koponen, Alhonen, Wong, Sirvio, and Castren, 2000).

The genetic and pharmacological manipulations described above alter BDNF signaling before learning. Thus, it is difficult to dissociate the role of BDNF in initial acquisition from that in long-term memory retention. Moreover, BDNF is involved in E-LTP and short-term memory (Alonso et al., 2002; Figurov et al., 1996), and therefore is likely to contribute to hippocampal processing of learning-related stimuli from the onset of training. Although studies of memory formation suggest that temporal phases of memory are dissociable mechanistically, it is unclear whether and how BDNF is involved in temporally distinct memory phases. An explicit test of

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BDNF in memory encoding would require a transient disruption of BDNF signaling at the time of acquisition or sequential manipulations in which BDNF levels are first decreased and then restored to baseline levels by the time of L-LTP onset.

Retention (storage) and recall (retrieval) of LTM

Investigating the role of BDNF during retention or recall of hippocampal dependent memory also requires an inducible or transient disruption of BDNF signaling. As discussed above, this cannot be determined using conventional BDNF or TrkB knockouts since deletion of these genes compromise initial acquisition. It has been shown that recall of some forms of hippocampal dependent memory increase BDNF mRNA expression, namely following contextual fear conditioning and Morris water maze training (Hall et al., 2000; Kesslak et al., 1998). Several studies have been designed to address the role of BDNF in the consolidation or recall of more remotely formed memories. Infusion of antisense BDNF oligonucleotides in rats that had been trained for the reference memory task for 28 days in the radial arm maze disrupts recall of a well-established spatial memory (Mizuno et al., 2000). In an inhibitory avoidance test, infusion of BDNF into the hippocampus 1 hr or 4 hrs after training facilitates, whereas that of anti-BDNF antibody at the same time after training impairs, LTM tested 24 hrs later (Alonso et al., 2002). Interestingly, infusion of BDNF antibodies or antisense oligonucleotide 6 hrs post-training no longer affects memory retention tested at 24 hrs (Alonso et al., 2002; Ma et al., 1998). However, one recent study showed that intra-hippocampal infusion of BDNF antisense oligonucleotide 12 hours after inhibitory avoidance training impairs memory retention 7 days later (Bekinschtein, Cammarota, Igaz, Bevilaqua, Izquierdo, and Medina, 2007). Thus, there are two time windows for LTM that require BDNF: one at 1-4 hours after encoding and this is critical for LTM lasting for 1-2 days, whereas the other at 12 hours after memory formation and is important for persistence of LTM 7 days later. Previous work has demonstrated the existence of two critical periods for memory consolidation, both of which require protein synthesis (Bourtchouladze, Abel, Berman, Gordon, Lapidus, and Kandel, 1998; Grecksch and Matthies, 1980; Igaz, Vianna, Medina, and Izquierdo, 2002). By extending the investigation of LTM beyond 24 hours, the authors revealed a previously unknown, time-delayed effect of BDNF expression on memory recall. This should encourage further investigation into the temporal parameters of BDNF-mediated plasticity and its role in LTM retention.

How could BDNF synthesis be induced 12 hours after memory acquisition when there is no obvious trigger? Replay of synaptic activity during consolidation (such as that during sleep) may be sufficient to elicit activity-dependent expression of BDNF (Foster and Wilson, 2006; Louie and Wilson, 2001). In fact, it is possible that the BDNF antisense oligos interrupted this replay of learning-related activity (Bekinschtein et al., 2007). On the other hand, there may be distinct phases of consolidation mediated by BDNF activity that are independent of experience and synaptic replay and are instead contingent on the induction of BDNF-dependent L-LTP. In other words, there are at least two distinct possibilities for post-acquisition involvement of BDNF signaling in the hippocampus: 1) BDNF synthesis and signaling is triggered by subsequent synaptic activity similar to that induced by initial learning or 2) the initial upregulation of BDNF during acquisition triggers a cascade of events resulting in subsequent BDNF-mediated consolidation processes that itself may recapitulate the learning-related activity. Further work is necessary to distinguish these possibilities.

Memory extinction

Extinction of previously acquired memories is a new form of learning and a potential target of BDNF-mediated plasticity. It has been shown that extinction of conditioned fear is accompanied by a significant increase in BDNF gene expression, particularly transcription mediated by BDNF promoters I and III in the prefrontal cortex (Bredy, Wu, Crego, Zellhoefer,

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Sun, and Barad, 2007) and amygdala (Chhatwal, Stanek-Rattiner, Davis, and Ressler, 2006). Moreover, extinction of fear-potentiated startle was impaired in mice with a site-specific knockout of the BDNF gene in the dorsal hippocampus through targeted injections of a cre-recombinase lentivirus (Heldt et al., 2007). Although it has not been tested, another potential target of BDNF modulation is the context-specific acquisition or retrieval of extinction memory (Corcoran and Maren, 2004). Many questions remain to be addressed. First, the role of BDNF in the encoding versus consolidation of extinction memory has not been determined and requires temporally restricted and inducible manipulations of BDNF signaling. As with initial learning, if BDNF plays a role in both, it will be difficult to observe the effect on consolidation if acquisition is compromised. Second, it is unclear whether BDNF transcription, or other aspects of BDNF signaling (trafficking, secretion, etc) is required, and if so, whether specific BDNF transcripts (exon I or III) are involved. Third, BDNF may contribute to specific aspect (s) of memory extinction by modulating synaptic function in specific brain regions. For example, amygdala-specific expression of a dominant-negative truncated TrkB receptor impairs consolidation but not encoding of conditioned fear extinction (Chhatwal et al., 2006). It is possible that hippocampal BDNF is required for acquisition of extinction memory. In contrast, BDNF in the amygdala or prefrontal cortex may be necessary for the consolidation and retention of extinction memory (Monfils, Cowansage, and Ledoux, 2007).

Dissociation of L-LTP and hippocampal dependent LTM

Although converging evidence demonstrates an important role for BDNF in the formation and maintenance of hippocampal-dependent memory traces, a few studies show inconsistent or contradictory results: some report significant impairments in spatial memory tested by Morris water maze, but not in rapidly acquired contextual memory of conditioned fear, in BDNF or TrkB mutant mice (Gorski et al., 2003; Heldt et al., 2007; Minichiello et al., 1999). Since it has also been shown that L-LTP can be induced without BDNF if multiple high frequency trains are used (Patterson et al., 2001), it is possible that BDNF-independent memory could form using signaling mechanisms that lead to BDNF-independent L-LTP in the hippocampus. While the stimulation protocol used to induce BDNF-dependent L-LTP (theta burst stimulation or TBS) is presumed to reflect physiologically relevant patterns of activation, there is very little data regarding the specific patterns of learning-related activity and how it differs in terms of resultant plasticity and memory formation. It is unknown whether or not BDNF-independent memory formation is driven by unique activity patterns or stronger activation of the hippocampus.

Behavioral tagging

Based on the investigations of BDNF regulation of L-LTP, there are several hypotheses that remain to be tested behaviorally. One of these is that BDNF-TrkB signaling may serve as a PRP-synaptic tag pair (Fig. 3). As discussed above, synaptic tagging allows for synapse specificity of plasticity and, under appropriate conditions, can generate heterosynaptic L-LTP if weak stimulation, sufficient to produce a synaptic tag, can capture PRPs induced by stimulation of an independent pathway. Evidence for “behavioral tagging” was recently reported in a study designed to test whether novelty exposure before or after weak training could provide the PRPs necessary to convert STM to LTM (Moncada and Viola, 2007). Weak inhibitory avoidance conditioning (IA) normally results in a STM memory detectable at 15 minutes, but not 1 or 24 hrs, after training. The same training produces LTM if coupled with novelty exposure. This effect was dependent on protein synthesis as infusion of anisomycin, a protein synthesis inhibitor, immediately after the pretraining exposure to novelty blocked the formation of LTM (Fig. 4). Because BDNF has been suggested to be a critical PRP, it would be interesting to test the sufficiency of this protein to induce LTM by replacing novelty exposure with a transient increase in BDNF expression. Likewise, the role of TrkB in synaptic

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tagging could be evaluated with a temporally restricted disruption of the receptor at the time of the weak training.

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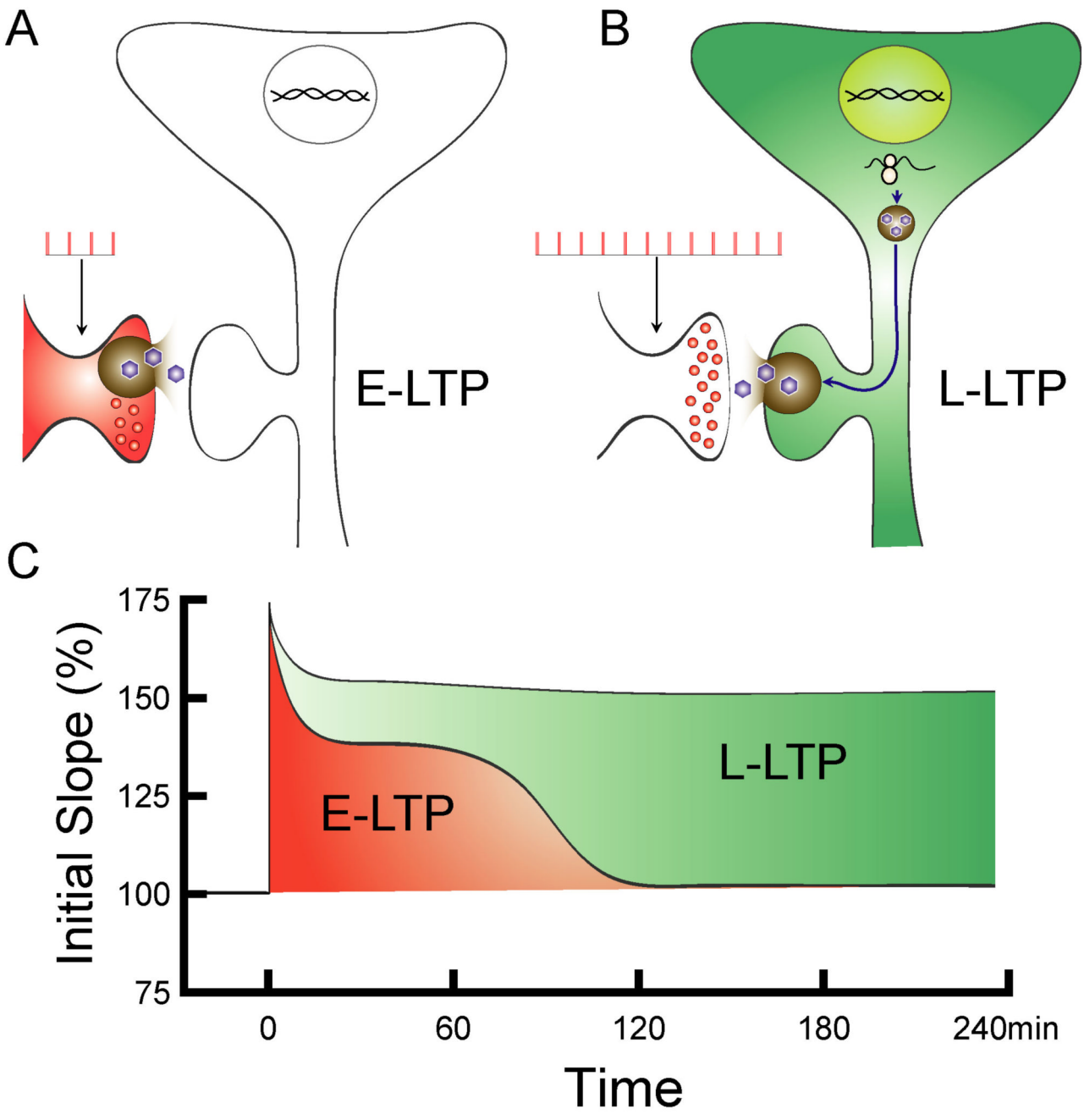

Figure 1.
Activity-dependent secretion of BDNF from presynaptic site (red in A and C) may be necessary for E-LTP, while the long-term maintenance of L-LTP requires sustained supply of BDNF through activity-dependent transcription and translation in the postsynaptic neurons (green in B and C).

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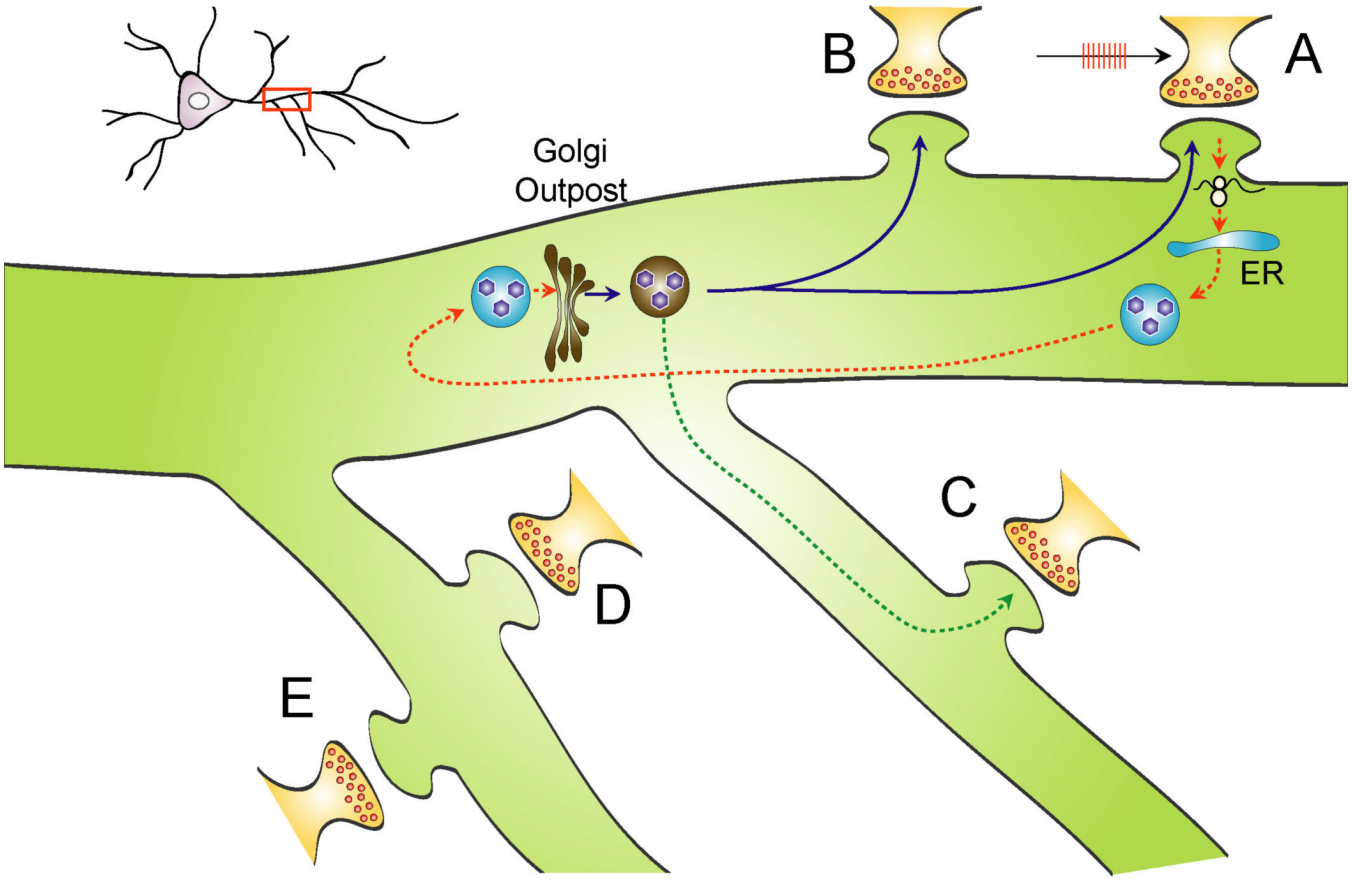

Figure 2. Synaptic specificity is lost after locally synthesized proteins at stimulated synapses are processed at Golgi apparatus elsewhere

When synapse A is stimulated with L-LTP inducing protocol, local protein synthesis is initiated. Since no Golgi apparatus is present at synapses, these proteins have to be delivered to Golgi in other places for processing, such as Glogi outpost at dendritic branch point. The newly processed proteins could be shipped back from Golgi to synapse A as well as synapse B on the same dendrite or synapse C on a different dendrite that share the same Golgi outpost. Synapses D and E are less likely to be affected.

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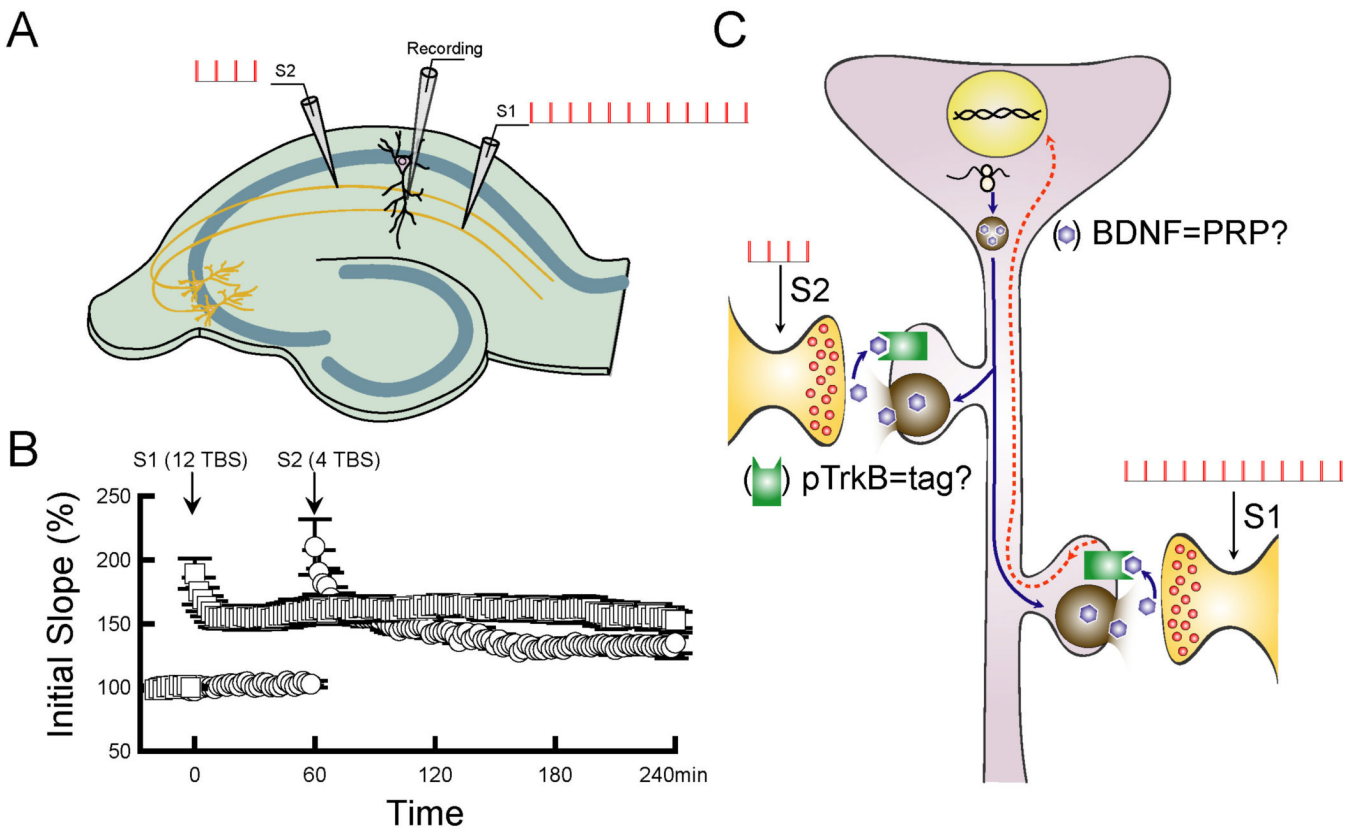

Figure 3. Synaptic tagging model

A, Two independent synaptic inputs to the same neuronal population are activated by two stimulating electrodes (S1 and S2). Field EPSPs are monitored by a single recording electrode in the Schaffer collateral region of the CA1. **B,** When one afferent pathway (S1) is activated by strong tetanus (12 theta burst at 100 Hz), a weak tetanus (4 theta burst at 100 Hz) applied to a second independent pathway (S2) to the same neuron usually induces L-LTP. **C,** Short-lived synaptic tag can be generated by strong tetanus and weak tetanus, while the PRPs can only be induced by strong tetanus. When one afferent pathway (S1) is activated by strong tetanus, a weak tetanus applied to a second independent pathway (S2) usually induces L-LTP because it creates a tag that captures the PRP induced by the strong tetanus in S1.

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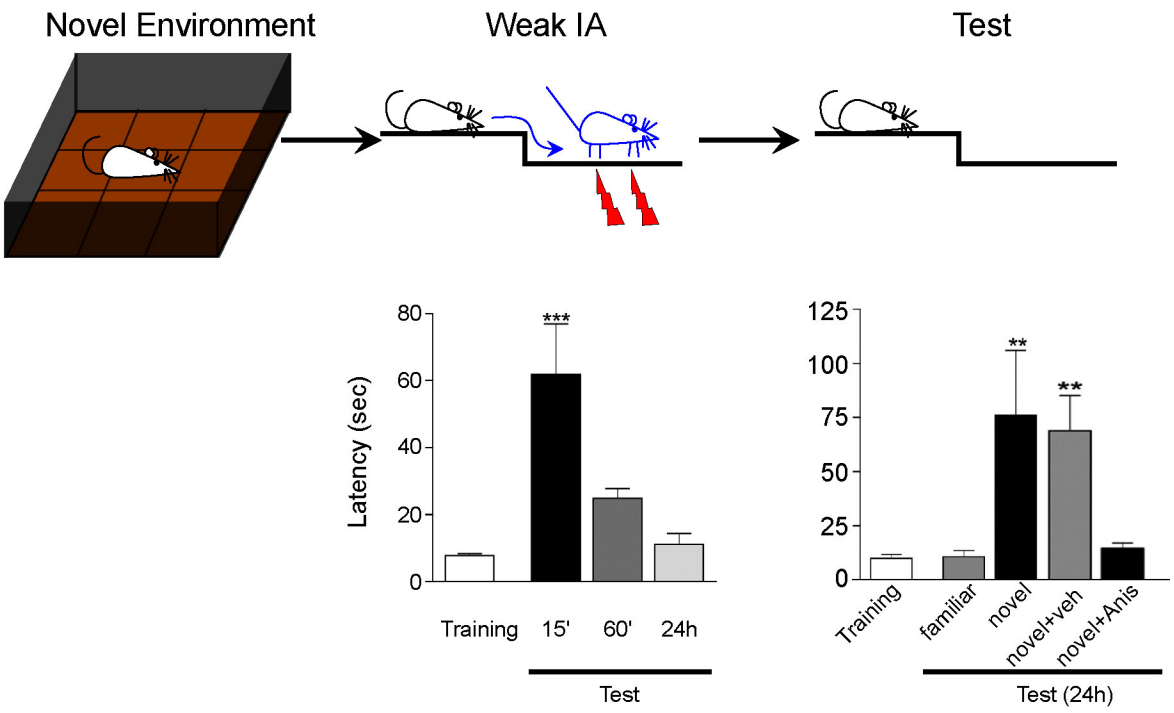

Figure 4. Behavioral tagging

A, Schematic diagram of experimental protocol. A rat was placed in a novel environment (open field) for 5 min within 1 hour before training for weak inhibitory avoidance conditioning (IA) and memory was tested at different time after weak IA conditioning. **B,** Weak inhibitory avoidance conditioning normally results in a STM detectable at 15 minutes, but not 1 or 24 hrs, after training. **C,** The same weak IA training produces LTM if coupled with novelty exposure. This effect was dependent on protein synthesis, since infusion of anisomycin, a protein synthesis inhibitorimmediately after the pretraining exposure to novelty blocked the formation of LTM, while vehicle control (novel + veh) still produces LTM. When the rat was familiarized with the novel environment before, the open field did not produce LTM when coupled with weak IA (familiar). (Modified from Moncada and Viola, J Neuroscience, 2007)