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REVIEW PAPER

Molecular Mechanisms of Early and Late LTP

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Abstract
LTP is the most intensively studied cellular model of the memory and generally divided at least two distinct phases as early and late. E-LTP requires activation of CaMKII that initiates biochemical events and trafficking of proteins, which eventually potentiate synaptic transmission, and is independent of de novo protein synthesis. In contrast, L-LTP requires gene expression and local protein synthesis regulated via TrkB receptor- and functional prions CPEB2-3-mediated translation. Maintenance of LTP for longer periods depends on constitutively active PKMζ. Throughout this review, current knowledge about early and late phases of LTP will be reviewed.

Keywords Ltp · Functional prions · Cpeb · Pkm zeta · Synaptic plasticity · Learning and memory

Introduction

Long-term potentiation (LTP), one of the most intensively studied cellular model of the memory, is defined as a long-term increase in synaptic response following a brief, high-frequency stimulation or other induction protocol. In 1966, Terje Lømo implied LTP for the first time [1]. Later, Tim Bliss and Lømo published their study which is acknowledged as the origin of the LTP field [2]. Bliss and Lømo showed that a brief high-frequency stimulation of the perforant path resulted in long-lasting potentiation of synaptic transmission, and they also made a very important discovery: they showed that LTP was saturable.

LTP has been defined in many different synapses in the brain and may manifest itself in many different forms in different synapses. Moreover, even with the same synapse, different forms of LTP can be revealed. For example, LTP is presynaptic in the synapses between the granule cells of the dentate gyrus and the CA3 pyramidal neurons and involves Ca^{2+} influx via voltage-gated Ca^{2+} channels (VGCCs) and cAMP-PKA signaling [3]. LTP is dependent on NMDA receptors (NMDAR) in synapses between the Schaffer collateral terminals and the CA1 pyramidal neurons and occurs predominantly by postsynaptic modifications, but different LTP forms that depend on VGCC and metabotropic glutamate receptors can be revealed by using different stimulation parameters [4, 5]. Much of the work deals with NMDAR-dependent LTP because this form of LTP is a suitable model for associative learning and this specific LTP form will be our focus throughout the review.

Biochemical events that are activated with a short tetanus and initiate LTP are called induction. The events that occur following induction and lead to long-term changes in synaptic activity are referred to as expression.

LTP has an early phase which is independent of protein synthesis (E-LTP), and a late phase (L-LTP) which involves the activation of transcription factors, is dependent on protein synthesis, and in which the structural changes are evident. A single brief tetanus leads to E-LTP that lasts up to 1–3 h, intermittent and repetitive applications (or a single stronger tetanus) produce L-LTP that lasts at least 24 h [6–8]. This review aims to present an integrative view to the mechanisms of induction, expression, and maintenance of LTP. Thus far, most recent reviews [9–11] focused on early phase. In this review, we begin with early phase, and then continue with activation of transcription factors and gene expression, control of translation, and finally, discuss maintenance mechanisms of LTP.

Early studies revealed that the characteristics of LTP matching the Hebbian learning rules [12]. While weak excitatory stimuli cannot produce LTP, simultaneous stimulation of multiple afferent axons may exceed the threshold required for LTP (cooperativity). In addition, when a

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stimulus that is too weak to induce LTP alone is presented with a strong stimulus, it achieves to produce LTP (associativity) [13, 14]. Another key property of LTP is its *input specificity*. These properties stem from the specific characteristics of NMDARs. At negative membrane potentials, the pore of NMDAR is blocked by Mg^{2+}. Depolarization displaces Mg^{2+} from the pore, allowing Na^{+}, K^{+}, and Ca^{2+} to pass. NMDARs conducts ions only when glutamate is bound and the membrane is depolarized enough to displace Mg^{2+}, and thus, work as a coincidence detector that detects presynaptic neurotransmitter release and postsynaptic depolarization. When one of two independent synapses of the same CA1 neuron is stimulated tetanically, LTP is induced in only the stimulated synapse. When L-LTP is induced in one of the synapses, a single brief tetanus in other synapses, normally expected to induce E-LTP, is sufficient to elicit L-LTP under these conditions [15]. Considering that L-LTP involves gene expression and protein synthesis, to explain how synapse-specificity can be achieved, synaptic tagging and capture (STC) hypothesis has been proposed suggesting that plasticity-related proteins (PRPs), produced either in soma or dendrites, are sent cell-wide, but can only be used in synapses tagged by synaptic activity [15, 16]. This hypothesis was supported by a number of studies that were conducted with *Aplysia* and rodent hippocampus.

Induction of LTP

For the activation of NMDA receptors in the induction of LTP, it is necessary that the postsynaptic neuron is depolarized while glutamate is bound. With the activation of NMDAR, Ca^{2+} influx activates signaling pathways that will eventually lead to synaptic modifications. LTP is often induced by tetanic stimulation (100 Hz, 1 s) of Schaffer collaterals (High-frequency stimulation, HFS). θ-burst stimulation and spike-timing-dependent plasticity, which is based on the matching of the action potential (AP) of presynaptic and postsynaptic neurons with an appropriate timing, was proposed to induce LTP as more appropriate stimulation methods because tetanic stimulation is not suitable for physiological activity [17]. LTP can be induced if the presynaptic AP is repeatedly produced shortly before the postsynaptic AP. This timing is critical for being able to provide maximum Ca^{2+} influx with NMDAR. If the postsynaptic neuron is stimulated first, it leads modest increases in calcium which preferentially activate phosphatases which have a higher affinity for Ca^{2+}/calmodulin (CaM) than does CaMKII, inducing long-term depression (LTD) [18].

Expression of LTP

The question of the underlying mechanisms of changes in synaptic transmission, i.e., expression is produced due to whether presynaptic or postsynaptic mechanisms, has occupied the field for a long time. The increase in synaptic activity in LTP may theoretically result from more transmitter release from the presynaptic terminal or greater response to the same amount of transmitter from the postsynaptic neuron or combinations there of. Since induction of LTP requires activation of the NMDA receptor, the postsynaptic neuron must transmit to presynaptic neuron that the LTP was induced in some way, if an increase in transmitter release in the presynaptic neuron is to occur. For this reason, a "retrograde messenger" to be released from the postsynaptic neuron and to change the function of the presynaptic neuron has been researched. Numerous studies have been conducted to reveal whether a change really occurs in presynaptic neurons [19–22]. These studies show that the expression of LTP is not caused by increases in glutamate released from the presynaptic neuron, and indicate that LTP is caused by changes in the postsynaptic neuron.

What are the postsynaptic mechanisms that lead to an increase in synaptic transmission? The answer to this question began to emerge with the discovery of silent synapses. During development, some synapses are insufficient for neurotransmission until they are activated by an appropriate stimulus [23]. Silent synapses in the CA1 region indicate that there is no EPSC as a result of excitatory stimulus in the resting membrane potential, but that it becomes evident following depolarization. It is thought that these silent synapses contain NMDARs but do not contain AMPARs [23]. The absence of AMPAR makes the synapse "silent" on physiological conditions. In these synapses, after LTP induction, synapse becomes competent for neurotransmission by AMPAR insertion to postsynaptic membrane [24, 25]. These findings led to the idea that strengthening both the silent synapses that do not contain AMPARs and the synapses that previously contain AMPARs with LTP was implemented by adding AMPARs to the membrane by exocytosis [26, 27]. Exocytosis takes place in the perisynaptic regions rather than directly in the synapse, where it is captured by the membrane by lateral diffusion [28].

What are the mechanisms that result in AMPAR insertion into the membrane by Ca^{2+} influx into the cell following NMDAR activation? Because Ca^{2+} flow is critical for the induction of LTP, research has been focused on calcium-dependent enzymes that may alter the function and structure of dendritic spines. CaMKII, which is found in very high concentrations in the brain, is activated by Ca^{2+} influx into the cell, and phosphorylates a large number of proteins, including AMPAR. Other than CaMKII, which is shown to be required for LTP, a number of proteins have been shown to contribute to LTP, including calpains, which is another Ca^{2+} dependent enzyme, PKA, different PKC isoforms, MAPK, tyrosine kinases [29–31]. These signaling pathways are extremely complex in LTP and their dominant roles

vary in different phases of LTP. The review will continue with a review of the different and major signaling pathways involved in E-LTP and L-LTP.

Molecular Mechanisms OF E-LTP: Role of CaMKII

Ca^{2+}/CaM-dependent protein kinase II (CaMKII) is a large holoenzyme composed of two overlapping hexameric rings that comprise 12 subunits. The rodent brain predominantly contains CaMKIIα and CaMKIIβ subunits, and CamKIIα homomers constitute the majority. CaMKII mRNA is transported to the dendrites and translated locally [32]. Each subunit has a C-terminal association site, which together forms a central core, with the N-terminal catalytic domains extending radially out of the central hub.

When CaMKII is autoinhibited, the regulator segment acts as a pseudosubstrate and suppresses the catalytic effect. Following the binding of the Ca^{2+}/CaM complex, the regulatory segment is removed so that substrate phosphorylation and CaMKIIα T286 autophosphorylation can occur [33]. If T286 autophosphorylation does not occur, the enzyme rapidly returns to its inactive state due to decrease in Ca^{2+} concentration. However, when T286 phosphorylation occurs, the enzyme remains active even after the Ca^{2+} concentration has returned to resting state [34]. Restricting CaMKII catalytic activity is phosphorylation of T305 and T306 residues of CaMKIIα Ca^{2+}/CaM binding domain, which occurs subsequent to T286 autophosphorylation, thereby preventing its activation by Ca^{2+}/CaM [35].

CaMKII has profound effects on both basal transmission and LTP. Deletion of CaMKIIα, but not of CaMKIIβ, decreases AMPAR- and NMDAR-mediated EPSC [36]. The absence of both CaMKII subtypes causes a further decrease in the AMPAR-mediated EPSC, but no further decrease in the NMDAR-mediated EPSC [36].

Activation of NMDAR and increase in Ca^{2+} concentration leads to the activation of CaMKII by Ca^{2+}/CaM, and the sequence of biochemical events leading to LTP of AMPAR-mediated EPSC begins. Deletion of CaMKIIα and/or β, or disruption of T286 autophosphorylation eliminates LTP [36]. CaMKIIβ does not affect basal transmission, but it still abolishes LTP [36]. If the active CaMKII is presented into CA1 cells, EPSC response increases and more LTP cannot be induced by synaptic stimulation [37, 38]. These results, together with the fact that LTP reaches saturation after a certain level, show that CaMKII is sufficient and necessary for LTP induction.

CaMKII translocates to synapse after activation by Ca^{2+}/CaM. Activated CaMKII binds to the NR2B subunit of NMDARs and phosphorylates target proteins in postsynaptic density (PSD) [39]. The crucial importance of CaMKII/NMDAR complex has been shown by that the mutations of binding sites on both CaMKII and NR2B impair LTP [40, 41]. Even constitutively active CaMKII (T286D-T305A/T306A) is lost its ability to potentiate AMPAR-mediated EPSC when NMDAR binding is prevented by I205K mutation [36]. Binding to NR2B also locks the enzyme in active conformation [42]. The number of NMDAR is independent of the size of the synapse (unlike AMPAR, the number of which is proportional to the synapse size), so it is considered that NMDARs reaching saturation for CaMKII is one of the limiting factors in inducing LTP [43]. In summary, for potentiation of AMPAR-mediated currents, there is a need of CaMKII with intact catalytic activity, forming a complex with NMDAR. Then, CaMKII is set in a close apposition to interact with its substrates.

Potentiation of AMPAR-Mediated EPSC

Enhancement of synaptic transmission occurs through the increases of the both number and single-channel conductance of AMPAR at PSD [44]. This increment AMPARs come from both extrasynaptic regions that constitute a ready receptor pool and intracellular vesicles that are inserted to the perisynaptic sites of the membrane by exocytosis [28]. AMPARs are highly mobile and diffuse freely into and out of the synapse until they are captured by the scaffolding proteins that contain PDZ domain (mainly PSD95) at PSD. AMPARs reach to the synapse by lateral diffusion. Prevention of lateral diffusion by cross-linking surface AMPARs, thus immobilizing them, impairs LTP [45]. CaMKII is though to activate both AMPAR insertion and capture.

Among the downstream targets of CaMKII are AMPAR and transmembrane AMPAR-regulatory proteins (TARPs). CaMKII and C-tail of GluR1 subunit of AMPAR have a long history in LTP. C-tail of GluR1 contains several phosphorylation sites for CaMKII, PKC and PKA [46–49]. S831 phosphorylation by CaMKII increases during LTP, leading an increase in AMPAR conductance [50, 51]. S845 phosphorylation by PKA is also important as shown by S831A mutants show normal LTP, whereas S831A–S845A mutant mice have impaired LTP [52, 53].

GluR1 C-tail phosphorylation by CaMKII is also thought to increase AMPAR trafficking into the membrane [54]. In a study where AMPAR subunits overexpressed, revealed that GluR1 homomers (normally constitute only a minority of total AMPARs) recruited to synapse during LTP, whereas GluR2-3 receptors are inserted to synapse in a constitutive fashion [55–57]. GluR2-lacking AMPARs are calcium-permeable and have an inward rectifier property. Thus, recruitment of GluR1 homomer AMPARs is evidenced by the degree of rectification. Supporting GluR1-centric model are the findings that LTP was impaired in the absence of GluR1, but was normal in GluR2 and GluR3 lacking mice [58, 59].

To achieve potentiation, AMPARs must be captured by scaffolding proteins to stabilize AMPARs in the PSD.

AMPARs are associated with TARPs, auxiliary proteins that play critical roles in AMPAR functions and trafficking [60]. As CaMKII targets, TARPs have numerous phosphorylation sites in their C-tail and are implicated in the process through which AMPARs are trapped in the PSD. TARPs contain PDZ binding domain in their C-tail that can bind PDZ domains of PSD95 [61]. TARP family member Stargazin (TARPγ-2) C-tail is positively charged that render it to interact with negatively charged phospholipids [62]. Phosphorylation by CaMKII disrupts this interaction to allow Stargazin to bind PSD95, trapping the AMPAR in the PSD [63, 64]. A study identified TARPγ-8 as a substrate for CaMKII and a crucial mediator of LTP, rather than TARPγ-2/3/4 [65]. S277 and S281 residues of TARPγ-8 are major phosphorylation sites by CaMKII and mutations of these residues impairs LTP, without affecting basal transmission and protein levels in PSD or extrasynaptic regions [65]. In contrast, mice with phospho-null TARPγ-2 alone or with γ3–4 knockout (KO) show normal LTP [65]. These results are inconsistent with previous ones where TARPγ-2 was an important mediator for retaining AMPAR. Further research is needed to elucidate these inconsistencies. Phosphorylated TARPγ-8 is thought to mediate AMPAR retaining by its interaction with PSD95 through the PDZ binding domain. However, in a study deletion of the PDZ binding domain of TARPγ-8 did not affect LTP, suggesting PDZ-independent mechanisms for TARPγ-8 [61]. But, this is controversial and could be due to compensation by other TARP members (see below).

Although all pieces of evidence above indicate that AMPARs and their auxiliary subunits TARPs are direct substrates for CaMKII, a study led to questioning the importance of all these findings. That study, using molecular replacement strategy, showed that previously implicated residues of GluR1 C-tail were not essential for LTP [66]. Moreover, homomeric GluR2 and kainate receptors (KAR) and their auxiliary Neto subunits performed normal LTP [66]. Although it does not necessarily exclude GluR1 C-tail- and TARP-dependent mechanisms summarized above, it shows there must be other constraints for LTP expression. A widely accepted explanation for this is "slot" hypothesis of LTP. According to this hypothesis, PDZ domain-containing synaptic scaffolding proteins (e.g. PSD95) serve as slots for AMPARs, which are unavailable under basal conditions and become available following LTP induction [67]. Thus allowing PDZ binding domain-containing proteins to bind PSD95. A recent study presented strong evidence for slot hypothesis. KAR/Neto complex, like AMPAR/TARP, contains PDZ-binding motif and binds PSD95 [68]. This study showed that PDZ interactions were essential for both basal transmission and LTP. In the absence of PDZ binding domains, both AMPAR/TARP and KAR/Neto complexes failed to bind PSD95 [68]. Therefore, both basal transmission and LTP are abolished. The authors concluded that the minimal requirement for LTP is the PDZ interactions of receptors/auxiliary subunits and PSD proteins [68]. These results also explain why KAR exhibits normal LTP. The remaining question is how slots become available to acknowledge receptors.

Regulation of Slots and Structure of Spines During LTP

LTP is associated with rapid enlargement of the spines in synapse-specific manner that occurs synchronized with increased EPSCs [69]. This enlargement is based on actin polymerization. Thus, it is sensible to think that the expansion of the synapse leads to enhanced trapping of AMPARs in PSD. However, remodeling of PSD is independent and PSD95 content does not increase until late phase of LTP, indicating the slot proteins are modified to accommodate more AMPARs without a change in their number [69]. Indeed, the number of PSD95 exceeds of AMPARs and NMDARs [70]. Recent findings demonstrate that the availability of slots is regulated through competitions of different PDZ binding domain-containing proteins.

SynGAP is a Ras/Rap GTPase-activating protein (GAP), highly enriched at PSD and a target for CaMKII [71]. SynGAP-α1 isoform contains PDZ binding domain and can occupy PSD95 under basal conditions [67]. Phosphorylation of SynGAP by CaMKII during LTP decreases its affinity for PSD95 and cause dispersion of it away from spines, allowing other proteins such as TARPs to bind PSD95 [67]. Therefore, SynGAP phosphorylation may be the permissive step for slot availability. SynGAP dispersion also decreases its RasGAP activity, leading to activation of Ras [71]. Ras/ERK signaling is shown to be critical for AMPAR delivery [72]. Moreover, phosphorylation of SynGAP by CaMKII shifts its GAP activity to inactivation of Rap which mediates AMPAR removal, thus, may contribute to LTP [72, 73]. SynGAP dispersion is also related to spine enlargement [71]. SynGAP knockdown (KD) causes spine enlargement and increased levels of AMPARs, which occludes further LTP induction, whereas phospho-null SynGAP causes decreased spine size and AMPAR number and prevents LTP induction [67, 71]. These findings support the notion that SynGAP regulates slot availability and spine enlargement.

Additional two key targets of CaMKII are Kalirin-7 and Trio-9, two highly homologue Rho guanine exchange factors (RhoGEFs) that activate Rho GTPases such as Rac1, Cdc42, RhoA [74]. Activation of Rho GTPases is critical for remodeling of actin cytoskeleton during LTP [75–77]. KD of Kalirin or Trio alone does not prevent LTP induction, although have some effects [74]. However, simultaneous inhibition of both prevents LTP [74]. Therefore, Kalirin and Trio phosphorylation by CaMKII is required for LTP,

and they perform overlapping functions [74]. Figure 1 summarizes the effects of CaMKII during E-LTP.

Regulation of AMPAR Trafficking

The strength of synaptic transmission depends on relative rates of endocytosis, exocytosis, and retention of AMPARs in PSD. As we have seen, during LTP, exocytosis rate increases. As we will see, neurons also have mechanisms that decrease endocytosis rate to potentiate transmission. Finally, neurons can direct endocytosed AMPARs back to the membrane via recycling endosomes [78].

Exocytosis depends on proteins which are parts of vesicle fusion machinery. Motor proteins MyosinVa/b and KIF1C are involved in delivering recycling endosomes to the membrane [79–81]. Synaptotagmins are Ca^{2+} sensor in exocytosis, and among the key proteins for AMPAR insertion during LTP [82]. Synaptotagmin-1 (Syt1) and synaptotagmin-7 (Syt7) are specifically involved in LTP, and the absence of both Syt1 and Syt7 in CA1 neurons, but not of either alone, abolishes LTP, without affecting basal transmission [82]. Block of LTP can be rescued by Syt7 expression, but not by mutated Syt7 which is incapable of binding Ca^{2+} [82]. Findings demonstrate that binding of Ca^{2+} to Syt7 is necessary but not sufficient for LTP, because, while Ca^{2+} influx through NMDARs still present, disrupting CaMKII function blocks LTP. Thus bringing the possibility that Syt1 and Syt7 are substrate for CaMKII. Further researches are needed to reconcile these results. Synaptotagmins do not function alone, but work with complexin, a co-factor for synaptotagmins [83]. In line with that, similar results are also observed when postsynaptic complexins are depleted, that is, LTP is blocked and basal constitutive transmission is not affected [84]. Synaptobrevin-2, SNAP-47, and syntaxin-3 which complexin binds strongly are shown to be required for regulated AMPAR exocytosis in LTP, but, except for synaptobrevin-2, not for constitutive basal AMPAR exocytosis [85].

Recycling endosomes are under the control of proteins such as GRIP1, GRASP1, PICK1 that determine AMPAR number. As we will see, these proteins are important targets for maintaining LTP and long-term memory.

Glutamate receptor interacting protein 1 (GRIP1) is a multi-PDZ domain-containing protein and interacts with GluR2 subunit in a phosphorylation-dependent manner, with phosphorylation of S880 and T876 residues of GluR2 disrupts GRIP1-GluR2 interaction [86–88]. The role of GRIP1 in AMPAR insertion is shown by its interactions with different binding partners, but it is still poorly understood. GRIP1, through its interaction with liprin-α which binds to KIF1A, is shown to be important for AMPAR delivery [89, 90]. A recent study suggested a new model in which GRIP1 acts as a bridge by binding GluR2 and ApoER2 to form a complex consisting of ApoER2, ephrinB2, and AMPAR [91]. This complex forms following neuronal activity and leads to insertion of new AMPARs to the membrane [91].

GRIP-associated protein 1 (GRASP1) is a neuron-specific RasGEF associated with GRIP1 and AMPAR [92]. GRASP1 is suggested to promote the transition from Rab4- to Rab11-positive mature recycling endosomes destined back to the membrane by exocytosis [93]. Neuronal activity leads an increase in the amount of GRIP1 and GRASP1 and increases their interactions with GluR1-2 [94]. Compatible with suggested functions of GRASP1,

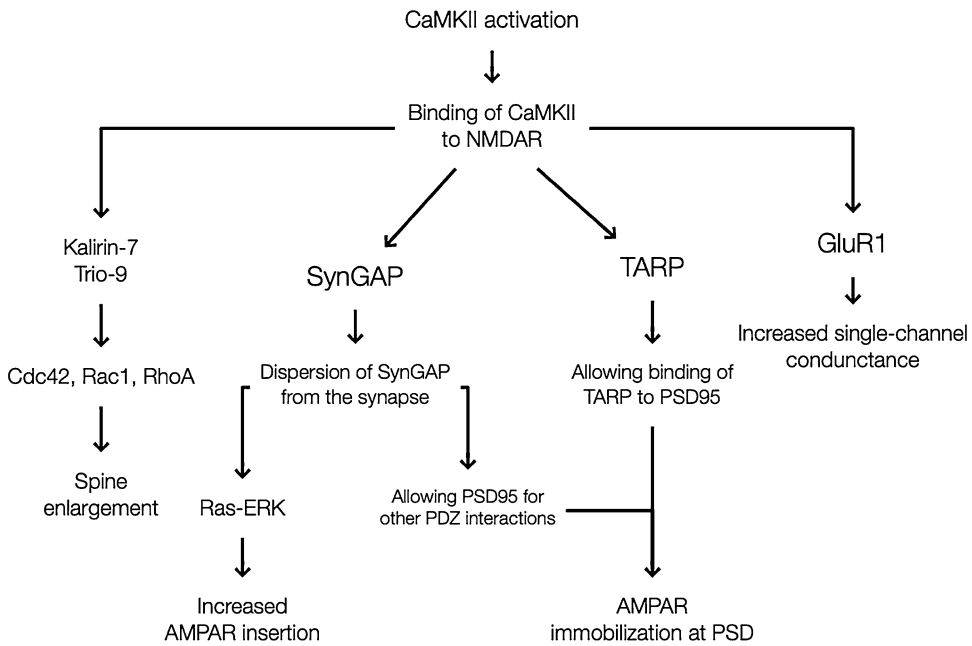

Fig. 1 Targets of CaMKII and their downstream effects

mutated GRASP1 causes accumulation of AMPARs in recycling endosomes and prevents normal AMPAR delivery to the membrane, resulting in impaired LTP and cognitive functions [94]. The importance of GRASP1 is further demonstrated in the maintenance of LTP which we discuss later.

Protein interacting with C-kinase 1 (PICK1) is a PDZ and BAR domain-containing protein that promotes AMPAR internalization by interacting with C-tail of GluR2 subunit, the same site that GRIP1 also binds [95]. A recent study suggested that PICK1 makes direct interactions, in NMDAR-dependent manner, with AP2 complex and dynamin, endocytic proteins required for AMPAR endocytosis [96]. Different roles have been proposed for PICK1, due to its versatility. PICK1 is also an important target for maintenance of LTP.

Molecular Mechanisms of l-ltp: From Synapse to Nucleus

Repeated synaptic stimuli lead to L-LTP, which lasts up to 24 h in vitro. This phase is dependent on changes in gene expression and de novo protein and mRNA synthesis. During L-LTP structural changes becomes apparent and the formation of new synapses occurs in young animals [97–99]. L-LTP requires PKA, MAPK and CREB in Schaffer collateral synapses [6, 100, 101].

cAMP-PKA-CREB

The hippocampal cAMP/PKA pathway is mainly activated by two mechanisms: Ca^{2+}/CaM sensitive adenyl cyclase (AC) activation via Ca^{2+}/CaM [102] and ligands that activate G protein-coupled receptors that stimulate AC [103]. cAMP binds regulatory subunits of PKA and releases catalytic subunits. PKA then moves to the nucleus and phosphorylates CREB, and allows it to function as a transcription factor. Thus, the transcription of genes related to CRE and involved in L-LTP begins [104].

In order to investigate the role of PKA and CREB in L-LTP, mice bearing genetic mutations both in PKA [7] and in CREB [105] were produced. Both of the two mutant mouse strains had severe defects in long-term memory and L-LTP, but E-LTP was normal. In another study, AC activator forskolin administration increased glutamate response and this response was blocked by PKA inhibitor [106]. In addition, increase in synaptic activity due to chemical activation of cAMP/PKA prevented LTP induction by electrical stimulation, indicating they both act through the same mechanism [107].

MAPK

Another critical pathway for L-LTP is MAPK [108]. PKA induces the association between Rap-1 and B-Raf and then B-Raf provides MEK phosphorylation, which in turn phosphorylates MAPK [109, 110]. MAPK can also be stimulated in different ways, such as CaMKII and cAMP-induced BDNF-TrkB signaling [72, 111]. The effect of MAPK activation on L-LTP requires nuclear translocation of MAPK and involves translation and transcription [112, 113]. MAPK has two major transcription factor targets: CREB and Elk-1 [114]. After activation of CREB and Elk-1 transcription factors, they bind to target regions in IEG (Immediate early genes) DNA sequences associated with synaptic plasticity. Transcription of these genes rapidly and transiently increases in response to LTP induction [114].

In the next two subsections, to illustrate the process, we will briefly discuss the regulation of Zif268 and Arc, the two IEGs that came into prominence, and their roles defined in L-LTP.

IEG: Zif268, A Transcription Factor

Zif268 (Egr1) is a transcription factor in early growth response (Egr) family that control expression of numerous genes and growth and function of the cell, and is an IEG [115]. Zif268 contains three zinc finger sequences in the DNA-binding domain so that it regulates transcription of other genes [116]. Expression of Zif268 gene is strongly dependent on neural activity, especially on NMDAR activation [115, 117]. The Zif268 gene promoter contains six SRE sequence to which Elk-1 can bind, and at least one CRE sequence to which CREB can bind [115]. In this respect, Zif268 expression can be regulated strongly by MAPK-Elk-1&CREB and PKA-CREB pathways.

LTP induction results in a strong and rapid increase in Zif268 transcription [118]. The increase in Zif268 mRNA occurs between 10 min and 2 h following LTP induction, depends on NMDAR activation and is related to protein synthesis-dependent L-LTP [119–121]. Evidence for the important role of Zif268 in L-LTP manifested by the examination of Zif268 mutant mice [122]. The absence of Zif268 in mutant mice does not affect the early phase of LTP, but inhibits its maintenance for the late phase.

Zif268 initiates a second gene expression wave involved in signaling, synapse formation, proteasome and transcription factors that include Zif268 itself [123]. Zif268 has a critical role in protein synthesis-dependent plasticity and it constitutes a convergence point between synaptic activity and genomic answers through cAMP-PKA-CREB and MAPK-Elk-1 & CREB pathways. However, there is a need for more detailed work on Zif268 target genes.

IEG: Arc

Another IEG is Arc (activity-regulated cytoskeleton-associated protein). Arc's expression is tightly linked to synaptic activity, and after induction of LTP, Arc protein and mRNA is rapidly transported to the dendrites, where it is locally translated [124–126]. Induction of LTP, as we shall see, leads to BDNF release, and Arc translation increases due to activation of TrkB receptor and later mitogen-activated protein kinase-interacting kinase (MNK) [127]. The Arc promoter contains CRE and SRE sequences that allow the binding of transcription factors such as CREB, SRF and Elk-1 [128] and its transcription requires activation of PKA and MAPK [129].

Unlike Zif268, Arc is not a transcription factor, but one of the main factors that regulate structural and functional plasticity [128]. Arc regulates synaptic activity bidirectionally with different partners involved in both LTP and LTD, and Arc is required for the stabilized L-LTP phase. With LTP induction, structural changes due to actin polymerization occur in the volume of dendritic spines. Arc plays an important role with its interaction with different proteins in actin polymerization.

Arc affects the phosphorylation state of cofilin during LTP consolidation [130]. Cofilin is a protein that leads to the depolymerization of actin. Arc leads to phosphorylation of cofilin by an unknown mechanism and inhibits its binding to actin, thereby providing actin stabilization [131]. Another protein that Arc interacts with is drebrin A, which competes with cofilin to bind to actin filaments and stabilizes the actin [132]. Arc undergoes SUMOylation during LTP consolidation and interacts with drebrin A by directly binding [132]. Thus, SUMOylated Arc can provide actin stabilization by allowing drebrin A to bind to actin and at the same time separating cofilin from actin [133].

Arc's role in LTD occurs by interacting with endocytic proteins such as endophilin-3, dynamin 2 and AP2 complex, reducing the number of AMPAR in synapses [134, 135]. The bidirectional effect of Arc on synaptic plasticity is regulated by post-translational modifications. Following induction of LTP, Arc's SUMOylation is increased and it provides actin stabilization by forming a complex with drebrin A. Non-SUMOylated form of Arc mediates the reduction of synaptic activity by promoting AMPAR endocytosis [133].

A very interesting discovery about Arc is its preferentially targeting inactive synapses which is due to the fact that Arc has a higher affinity to inactive CaMKIIB than its active form [136]. This targeting of Arc to inactive synapses has led to a new model called *inverse* STC which posits Arc serves as a tag for those synapses to decrease their AMPAR levels, underscoring the contrast between stimulated and unstimulated synapses [136]. Inverse STC may work as a complementary to STC. Indeed, inverse tagging hypothesis is consistent with the synaptogenesis and synaptic elimination mechanisms and the notion that learning induces redistribution of limited synaptic resources [99, 137, 138].

In addition to its rapid transportation to dendrites, Arc has been shown to slowly accumulate in the nucleus, where it forms a complex with the nuclear matrix protein spectrin βIV, and promotes the formation of promyelocytic leukemia nuclear bodies, decreasing GluR1 transcription [139, 140]. Nuclear Arc is shown to be required for synaptic scaling [139]. Arc also function in chromatin remodelling by interacting with Tip60, a histone-acetyltransferase to promote gene expression [141]. However, much less is known about Arc's nuclear actions.

Regulation of Protein Synthesis

How does synapse-specific modifications occur when gene expression happens in the nucleus? STC hypothesis indicates that PRPs are sent cell-wide, but can only be used actively in synapses tagged by synaptic activity [15, 16]. A tag must initiate some local changes that allow the synapse to capture PRPs to produce long-term and synapse-specific modifications [142]. Dendrites contain machinery required for protein synthesis [143]. The factors involved in the regulation of local protein synthesis and their mechanisms will now be discussed.

Control of Translation and BDNF

Brain-derived neurotrophic factor (BDNF) is a small dimeric protein that acts through tropomyosin-related kinase B (TrkB), a receptor tyrosine kinase that it binds with high affinity. BDNF is found both in the presynaptic and postsynaptic regions in glutamatergic synapses [144, 145] and it is released in response to LTP inducing stimuli [146] however, the release zone have not been determined precisely. A recent study compared the contributions of presynaptic and postsynaptic BDNF and TrkB to LTP, by selectively deleting them in CA3 and CA1 [147]. Presynaptic BDNF is involved in LTP induction, when deleted causes stable but smaller LTP, whereas postsynaptic BDNF contributes to LTP maintenance, deletion of it leads to rapid decay of LTP [147]. Likewise, presynaptic TrkB receptor is involved in maintenance, and postsynaptic TrkB is required for LTP formation, deletion of TrkB in CA1 almost completely blocks LTP [147]. Other studies using glutamate uncaging has demonstrated the importance of postsynaptic release and autocrine signaling of BDNF [148, 149].

BDNF is an important regulator of synaptic plasticity and protein synthesis during LTP [150]. Although there are differences in the time periods during which the inhibitors are effective depending on the particular method of L-LTP induction, inhibition of protein synthesis or BDNF–TrkB

signaling eliminates L-LTP with similar kinetics [148, 151, 152]. Therefore, the effects of BDNF are largely, but not exclusively, assigned to its ability to regulate translational machinery. TrkB receptors activate ERK/MNK1 and phosphatidylinositol 3-kinase (PI3K)-Akt-mTORC1 pathways [153]. However, it is shown that BDNF causes more pronounced upregulation of PI3K–Akt pathway than ERK [111, 154]. Thus, enhanced local translation through BDNF is thought to rely on mTORC1 activation [for reviews see 155,156].

A downstream target of ERK is calpain-2, a protease that cleave phosphatase PTEN, a negative regulator of Akt [157]. Thus, calpain-2 activation by ERK leads to enhanced local protein synthesis via Akt–mTORC1. Calpain also degrades a Ras inhibitor protein SCOP [158]. However, degradation of SCOP stimulates its rapid mTORC1-dependent synthesis [158]. This pathway therefore has a self-inhibiting effect [159].

Glycogen synthase kinase-3 β (GSK3β) is a serine/threonine kinase that regulates synaptic plasticity bidirectionally and a substrate for Akt and PP1 [160]. During LTP, GSK3β is phosphorylated by Akt, decreasing its activity. In contrast, during LTD, GSK3β activity is increased via dephosphorylation of GSK3β by PP1 and inhibition of Akt [160]. It is also shown that inhibition of GSK3β by PI3K-Akt prevents synapses from undergoing LTD, preserving synaptic modifications [160].

BDNF also affects local protein synthesis through miRNA regulation by elevating the expression of Dicer endonuclease, which cleaves pre-miRNAs to produce mature miRNAs and of the RNA-binding protein Lin28a, which prevents the target pre-miRNAs from being converted to mature miRNAs [161]. ERK-mediated phosphorylation of TRBP, a binding partner of Dicer and Lin28a, increase stabilization of Dicer and Lin28a by forming a complex with them [162]. Thus, with this dual regulation, while BDNF generally promotes miRNA formation, it selectively prevents the formation of target miRNAs via Lin28a, upregulating proteins required for synaptic plasticity such as GluR1, CaMKIIα, Homer2 [161]. This mechanism confers selectivity to the translational effects of BDNF [161].

The importance of BDNF is further expanded by the pieces of evidence showing BDNF is a PRP and hence TrkB is a tag. BDNF is upregulated during L-LTP [111]. BDNF heterozygous mice show impaired STC and BDNF application can transform E-LTP into L-LTP [163, 164]. When L-LTP is induced in one synapse (S1), a weak tetanus on another synapse (S2), normally expected to induce E-LTP, can elicit L-LTP by capturing PRPs. Inhibition of TrkB receptors prevents capture and formation of L-LTP on S2 [152]. Interestingly, at the time of L-LTP induction, inhibition of TrkB on S1 blocks L-LTP on S1, without affecting capture on S2 [152]. This is because L-LTP inducing stimuli not only create a tag on that synapse, but also produces PRPs [152]. Thus, these results strongly indicate that BDNF is a PRP and TrkB is a tag.

Control of Translation and Functional Prions

Cytoplasmic polyadenylation element binding (CPEB) protein, which has prion-like properties, is essential for maintaining long-term memory and regulates local protein synthesis by activating dormant mRNAs [165, 166]. Series of studies conducted on *Aplysia* and *Drosophila* revealed that *Aplysia* isoform ApCPEB and *Drosophila* isoform Orb2 is required for maintenance, but not for initiation, of long-term memory and synaptic plasticity and their activation is regulated by neural activity [167–171].

There are 4 CPEB genes in humans and mice (CPEB1-4) [172]. Among these isoforms, CPEB2 and CPEB3 have amino-terminal prion-like regions [172]. CPEB2 can function as a repressor of translation during basal conditions, and as an activator after neural activity [173]. Hippocampal slices from CPEB2 conditional KO (cKO) mice revealed that whereas CPEB2 depletion does not effect E-LTP formation, it significantly diminishes L-LTP [173]. CPEB2 cKO mice also showed normal spatial learning, however, they had impaired memory consolidation [173]. CPEB2 cKO had decreased surface, but not total, AMPARs [173]. CPEB2 KO neurons had decreased GRASP1 levels, without a change of GRASP1 mRNA [173]. Thus, CPEB2 promotes translation of GRASP1, which is important for AMPAR recycling [173]. Other CPEB2 target mRNAs remain to be determined. Prion properties or regulation of CPEB2 have not been investigated in detail so far, only those of CPEB3 have been studied.

Like other prion proteins, CPEB3 has two conformational states: (1) repressor, monomeric, inactive state, and (2) self-sustaining, active, aggregated state. CPEB3 has been shown to bind to target mRNAs such as GluR1-2 and to suppress their translations in the basal state [174–176]. CPEB3 allows translation of target mRNAs after its monoubiquitination by ubiquitin ligase Neuralized1, during neural activity [177]. These findings together show that CPEB3 can function as a suppressor in the basal state and as an activator after undergoing posttranslational modifications.

CPEB3 forms aggregates in response to synaptic stimulation, and the transition from the monomeric state to the aggregated state is parallel to the transition from the inhibitory effect to activatory effect [176]. Investigation of memory maintenance of CPEB3 cKO mice revealed that CPEB3-mediated protein synthesis was needed to maintain memory, but not for acquisition of memory [175]. In line with that, CPEB3 cKO does not affect E-LTP, but inhibits L-LTP formation [175]. It was also shown that CPEB3 lost its function in result of deletion of prion-like amino acid

sequences [175]. All findings indicate that CPEB3 allows maintenance of memory by increasing the translation of target mRNAs by synaptic activity-dependent conformational changes that allow the CPEB3 to switch from the suppressor state to the activator state [176].

Because once the active aggregate was formed, CPEB3 can then incorporate monomeric CPEB3s into its structure due to the prion-like properties of CPEB3, inhibitor mechanisms that restrict the activity of CPEB3 were investigated, and the activity of CPEB3 was found to be restricted by SUMOylation [178]. In the basal state, CPEB3 is present in SUMOylated state and thus acts as a translational inhibitor in its monomeric form. In response to neural activity in the dendrites of hippocampal neurons, the SUMOylation of CPEB3 decreases and ubiquitin ligase Neuralized1 levels increase and lead to ubiquitination of CPEB3, resulting in the transition of CPEB3 to the active form, and thus translation of CPEB3 target mRNAs increases, which are critical for synaptic plasticity [177].

Increase in translation by CPEB occurs through polyadenylation, a process required for the conversion of silent mRNAs to mature mRNAs. Silent mRNAs contain a sequence called the cytoplasmic polyadenylation element. CPEB binds to this sequence to convert silent mRNAs into mature mRNAs by adding poly-adenine tail to silent mRNAs via polyadenylate polymerase (PAP) enzyme [179].

Finally, functional prion CPEB, with the properties defined above such as activity-dependent and spatially restricted modifications and being able to interact with mRNAs that change synaptic transmission, can be a key component of STC [171, 180].

Maintenance of LTP: PKMζ

Numerous molecules and signaling pathways mediating the initiation and consolidation of LTP have been identified and some have been addressed in previous sections. These molecules are active only in certain time periods and after that their inhibition does not reverse LTP. Consolidation, which is the process of converting short-term memory to long-term memory, requires new mRNA and protein synthesis, but there is a limited time window in which protein synthesis inhibitors are effective [155]. Is there a protein that has a continuous effect on the maintenance of LTP and long-term memory? The continuous enzymatic effect of the constitutively active PKMζ is thought to be the key molecule in the maintenance of LTP and long-term memory [181]. Direct delivery of PKMζ to CA1 cells strengthens neurotransmission more than all other known substances [182].

Protein kinase C (PKC) isoforms are divided into three families according to their sensitivity to second messengers and their structure: classical (cPKC), novel (nPKC) and atypical (aPKC). PKC is a monomeric protein with an N-terminal regulatory domain and a C-terminal catalytic domain. The N-terminal regulatory segment of PKC contains a pseudosubstrate region that inhibits the catalytic effect. PKC isoforms can be converted into the structurally active form as a result of the proteolysis of the regulatory subunit, and this structurally active form is called PKM. However, an aPKC isoform differs from the others on the grounds that it is synthesized without a regulatory segment. PKMζ, which is produced from the internal promoter of the PKCζ gene consists only of the catalytic segment, and it is constitutively active. PKMζ has an extremely critical role in the maintenance of LTP and long-term memory because of these properties.

PKMζ prevents AMPAR endocytosis and lateral diffusion away from the synapse to maintain LTP and long-term memory [182, 183]. Inhibition of PKMζ may eliminate LTP even after days and may even cause the deletion of a 1-month old spatial memory [181]. These findings indicate that PKMζ is more potent on LTP and long-term memory than all other known proteins.

How does PKMζ become activated, how is the translation of PKMζ maintained for a much longer period of time than its half-life, up to 1 month in vivo, what are the effects that PKMζ provides to protect synaptic plasticity over long periods of time?

Positive feedback-like mechanisms have been proposed to provide the PKMζ levels required to maintain LTP. The PKMζ mRNA is carried to the dendrites following transcription, but its translation is inhibited by a peptidyl-prolyl isomerase PIN1 [184, 185]. Following LTP induction, the activity of PIN1 diminishes and the suppressive effect on PKMζ translation ceases, then PKMζ maintains its own synthesis by phosphorylating PIN1 [185]. The mRNA levels of PKMζ do not change in LTP and long-term memory, so the increase in PKMζ level results from the translation of pre-existing mRNAs [186, 187].

Another mechanism by which PKMζ translation can be sustained is protein synthesis mediated by functional prion CPEB, discussed in the previous section. PKMζ mRNA is a target of ApCPEB in *Aplysia*, and Orb2 in *Drosophila* [170, 188]. A similar mechanism may also apply to mammals and maintenance of memory by this mechanism would be attractive, because of self-perpetuating properties of CPEB and autonomous activity of PKMζ.

The effects of PKMζ that enhance and protect AMPAR-mediated transmission are not yet fully characterized, but there is a built model. According to this model, PKMζ interacts with PICK1, a GluR2-binding protein that promotes AMPAR internalization, and NSF, another protein that binds to GluR2 that mediates AMPAR insertion [96, 189]. NSF regulates GluR2-PICK1 interaction and stabilizes AMPAR at synapse under basal conditions [190]. In addition to AMPARs that contain GluR2 in synapse,

extrasynaptic regions also contain a pool of AMPARs that contain GluR2 bound to PICK1. PKMζ forms a complex with PICK1 and enhances the effects of NSF, so that extrasynaptic AMPARs bound to PICK1 are integrated to synapse [191]. This model has been supported by a number of studies, but the targets of PKMζ are still unknown.

While the role of PKMζ in the maintenance of LTP and in long-term memory continued to be investigated, two studies led to the questioning of all previous findings about PKMζ [192, 193]. According to these studies, LTP and learning and memory processes of PKMζ KO mice were normal and PKMζ were not necessary for LTP and learning and memory. Moreover, the ZIP still eliminated LTP and long-term memory. Thus, the later investigations considered two possibilities: the PKMζ might not really be necessary for LTP and long-term memory, but the ZIP would still eliminate LTP and long-term memory by some means, or a compensation mechanism would develop in PKMζ KO mice and this mechanism could be inhibited by ZIP [194].

Still active effect of ZIP on PKMζ KO mice encouraged the investigation of possible compensatory effects of other PKC isoforms. Thus, the role of the other aPKC isoform protein kinase C iota/lambda (PKCι/λ) has come into play.

Since ZIP inhibits both PKMζ and PKCι/λ, it is not a suitable tool in distinguishing the roles of two kinases, and more specific inhibitors are needed. Therefore, the studies on which an aPKC is specifically targeted have been carried out [194, 195]. One of these studies used antisense that selectively targeted PKMζ mRNAs and an inhibitor that selectively targeted PKCι/λ. PKMζ-antisense administration inhibited both PKMζ increases on LTP and L-LTP in wild-type mice but had no effect on L-LTP in PKMζ-null mice [194]. These results support the hypothesis that PKMζ is required for LTP but a compensation mechanism develops in PKMζ-null mice [194].

What is the mechanism of compensation that is developed in PKMζ-null mice? The other aPKC that is expressed in the hippocampus, PKCι/λ, is the closest isoform to PKMζ and blocked by ZIP [194]. It is known that PKCι/λ increases translation and has a role in E-LTP, and it has been suggested that it may act as a compensator in PKMζ-null mice [196, 197]. PKCι/λ, which is transiently elevated in wild-type mice, rises steadily in PKMζ-null mice and is similar to the continuous translation of PKMζ in wild-type mice [194]. Since inhibition of PKCι/λ blocked E-LTP [197], to investigate its possible role in L-LTP, PKCι/λ antagonists were applied after L-LTP was established and it was found that they eliminated L-LTP in PKMζ-null mice but had no effect on wild-type mice [194]. The results of hippocampus-dependent long-term spatial memory tests also confirmed these findings [194]. When all findings considered together, they indicate that PKMζ is required for LTP, but that PKCι/λ compensation mechanism develops in PKMζ-null mice [194].

Can PKMζ be fully compensated by the effect of PKCι/λ? In general, making learning tests more difficult or the reduction of training resulted in deficits in spatial memory in PKMζ-null mice and it was found that the compensatory effect of PKCι/λ was not complete [194].

Another study aimed to determine the different functions of PKMζ and PKCι/λ in LTP, and used the KD approach to which PKMζ or PKCι/λ was targeted [195]. In this study, it was found that early expression of LTP decreased due to PKCι/λ KD, and L-LTP maintenance deteriorated due to PKMζ KD [195]. They also showed that PKCι/λ and PKMζ increased consecutively during LTP [195]. After 30 min of LTP induction, the active, phosphorylated PKCι/λ (p-PKCι/λ) significantly increases but returns to control level 2 h after LTP induction [195]. In contrast, PKMζ significantly increases after 2 h from LTP induction [195].

Thus, PKCι/λ is important for the early expression of LTP, in which the p-PKCι/λ levels increase, then the p-PKCι/λ levels decrease while the PKMζ levels increase during LTP maintenance [195]. However, it is not known how regular increases in PKCι/λ and PKMζ levels occur. In the same way, it is not known how PKCι/λ is engaged as a compensator in PKMζ KO. Finally, the specific effects of PKMζ have not yet been elucidated.

Conclusion

Significant progress has been made in the molecular mechanisms of LTP since its first definition by Bliss and Lømo in 1973. Especially in recent years, the pace of development has increased at an exciting level. LTP has at least two phases, E-LTP and L-LTP. E-LTP involves modification of existing proteins, independent of gene expression and protein synthesis. L-LTP requires new mRNA and protein synthesis, and its maintenance depends on CPEB2-3, which has prion-like properties, and ongoing long-term activity of PKMζ. The investigation of the contribution of functional prions and the PKMζ–LTP will significantly increase our knowledge of LTP in the upcoming period.

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