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Long-term potentiation: peeling the onion

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Abstract

Since the discovery of long-term potentiation (LTP), thousands of papers have been published on this phenomenon. With this massive amount of information, it is often difficult, especially for someone not directly involved in the field, not to be overwhelmed. The goal of this review is to peel away as many layers as possible, and probe the core properties of LTP. We would argue that the many dozens of proteins that have been implicated in the phenomenon are not essential, but rather modulate, often in indirect ways, the threshold and/or magnitude of LTP. What is required is NMDA receptor activation followed by CaMKII activation. The consequence of CaMKII activation is the rapid recruitment of AMPA receptors to the synapse. This recruitment is independent of AMPA receptor subunit type, but absolutely requires an adequate pool of surface receptors. An important unresolved issue is how exactly CaMKII activation leads to modifications in the PSD to allow rapid enrichment.

Introduction

One of the most remarkable features of the brain is it ability to store vast amounts of information. Changes in the strength of synaptic connections as a mechanism underlying learning and memory had been proposed by Cajal at the beginning of the last century and then formulated into a concrete synaptic model by Hebb in 1949. However, it was not until the discovery of long-term potentiation (LTP) (Bliss and Lomo, 1973; Lomo, 1966), in which brief high frequency synaptic stimulation in the hippocampus results in a long lasting increase in synaptic strength, that there was experimental evidence supporting such a proposal. LTP has remained to this day the most compelling cellular model for learning and memory. Indeed, there are no competing models in the field. In this review we discuss the minimal requirements for LTP and our current knowledge of the underlying molecular mechanisms.

Early days

The discovery of LTP in the dentate gyrus in vivo was soon followed by two additional major developments. First, was the demonstration that LTP could be induced in the

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hippocampal slice preparation (Schwartzkroin and Wester, 1975) and second, was the discovery that the NMDA subtype of glutamate receptor was required for hippocampal LTP (Collingridge et al., 1983). It is now well accepted that NMDAR-dependent LTP is widespread in the CNS.

Multiple forms of LTP

One of the problems in the LTP field is semantics. The field has never explicitly settled on a precise definition for this phenomenon. Perhaps the broadest definition would be a long-term (>30 min.) enhancement in synaptic transmission following brief high frequency synaptic stimulation, although, as discussed below, this is not strictly a requirement for NMDAR-dependent LTP. If we accept this broad definition, then it is clear that multiple forms have been described at different synapses. The clearest example is hippocampal mossy fiber LTP, a form of LTP that is universally agreed to be independent of NMDAR activation and to have an expression mechanism distinct from NMDAR-dependent LTP (Nicoll and Malenka, 1995; Nicoll and Schmitz, 2005).

The issue of multiple forms of LTP at excitatory synapses in the CA1 region is considerably more complex. It has been proposed that the properties of LTP depend on both the frequency and pattern of stimulation (e.g., 100 versus 200 Hz, theta burst stimulation etc) and on the stimulus strength. In addition it has been proposed that the properties of LTP change over time. For instance, a widely held model suggests that at some point after the induction of LTP (>1 hour), protein synthesis is required to maintain the potentiation (Johnstone and Raymond, 2011; Reymann and Frey, 2007; Schuman et al., 2006). However it should be noted that, although rarely cited, there have been a number of well controlled studies that have failed to find any dependence of LTP on protein synthesis up to 8 hours after the induction (e.g., (Abbas et al., 2009; Villers et al., 2012). To add to the apparent complexity, the list of proteins proposed to be involved in LTP continues to grow (well over a hundred) leading some investigators to despair as to whether LTP is a tractable phenomenon (Sanes and Lichtman, 1999).

What strategies are available to deal with the complexities and confusion in this field? First, the vast majority of studies on LTP have been carried out in the CA1 region where LTP is particularly robust. Given the possibility that differences might exist at different synapses in the brain, it would seem prudent to focus one's attention on the CA1 excitatory synapse where a large body of data already exists. Furthermore, it is generally agreed that it is the unique properties of the NMDAR that make LTP such a compelling model of learning and memory. Thus, while other forms of LTP may exist at CA1 excitatory synapses, it is NMDAR-dependent LTP that is of the greatest interest.

Approaches to studying NMDAR-dependent LTP

Part of the confusion in the study of LTP is the failure to appreciate that there are two separate questions regarding the induction of LTP. The first question is what controls the activation of the NMDAR and the second question is what happens after activation of the NMDAR? It is well established that there are only two requirements for the induction of LTP: glutamate binding to the NMDAR and membrane depolarization. Most studies have used various forms of tetanic stimulation, to cause the depolarization of the postsynaptic membrane. However, the effectiveness of the tetanus in depolarizing the neuron is influenced by a large number of variables. For instance, altering the level of GABAergic inhibition will have a profound effect on the degree to which a tetanus will depolarize the postsynaptic neuron and therefore NMDAR activation. In fact any manipulation that affects the level of depolarization (e.g., postsynaptic excitability, number of synapses activated, presynaptic transmitter release, etc.) and therefore the degree of NMDAR activation will

affect LTP, but this has nothing to do with understanding the central mechanisms underlying LTP. This confusion may well explain the long list of proteins postulated to mediate LTP (Sanes and Lichtman, 1999). To determine the requirements for LTP, the important question is what happens after NMDAR activation. Thus in order to study LTP in a controlled fashion, one must be able to precisely control the depolarization. This is accomplished by a "pairing" protocol. Specifically one uses cesium to block potassium channels in the postsynaptic neuron so the neuron can be held at a given membrane potential (e.g., ~0 mV) during synaptic stimulation.

The locus of change during NMDAR-dependent LTP

Although the primary mechanism mediating the induction of LTP, the activation of NMDARs, was elucidated rapidly and with unanimity, the mechanisms underlying the subsequent expression of LTP remained contentious for many years. In particular, it could not be agreed upon as to whether the enhanced synaptic transmission after LTP induction was due to a presynaptic increase in transmitter release or alternatively to a postsynaptic increase in the AMPAR response. There was considerable circumstantial evidence for a postsynaptic expression mechanism (Nicoll, 2003; Nicoll and Malenka, 1999), but the observation that during LTP the synaptic failure rate decreases (Bekkers and Stevens, 1990; Malinow and Tsien, 1990) strongly and abruptly swayed opinion to the presynaptic side. Based on classical quantal analysis such a change indicates an increase in the probability of transmitter release (Del Castillo and Katz, 1954). An equally abrupt change of opinion back to the postsynaptic side came with the discovery that some CA1 synapses are postsynaptically silent (i.e., synapses containing only functional NMDARs). During LTP these synapses rapidly acquire AMPAR responses so that the failure rate decreases. Thus this finding provides a postsynaptic explanation for the change in failure rate (Isaac et al., 1995; Liao et al., 1995). As a consequence a postsynaptic expression mechanism for LTP is now generally accepted and led into the era of studying the precise mechanisms that regulate AMPAR trafficking to synapses.

As is often the case in science, technical advances helped bring a final resolution to this debate. With the introduction of two-photon microscopy, one can image single spines, which receive excitatory synapses, and uncage glutamate onto single spines. Coupled with electrophysiology one can now perform a "pairing" experiment where the activation of NMDARs by uncaging glutamate onto a single spine can be coupled with postsynaptic depolarization. With this reduced system one can show a rapid enhancement of the AMPAR-mediated uncaging response that lasts for the duration of the experiment and is dependent on NMDAR activation (Harvey and Svoboda, 2007; Lee et al., 2009; Matsuzaki et al., 2004). At this level of resolution one can show that the LTP is, indeed, synapse specific, since close neighboring synapses are not potentiated. These experiments provide unequivocal evidence that LTP is accompanied by a postsynaptic enhancement of the AMPAR response. The experiments do not exclude a presynaptic component, but given that the magnitude of the enhancement is similar to that seen when LTP is induced with synaptic activation, there is no need to include a presynaptic component in the model. Another important advance resulting from these experiments is the observation of a rapid increase in spine volume that persists for the duration of the experiment (Harvey and Svoboda, 2007; Lee et al., 2009; Matsuzaki et al., 2004). This is now considered a robust and reproducible morphological correlate of synaptic plasticity.

How does NMDAR activation trigger LTP?

It is generally agreed that the influx of calcium through the NMDAR is required for LTP. There is also a consensus that CaMKII is the downstream target of calcium and that CaMKII

is both necessary (Giese et al., 1998) and sufficient (Lledo et al., 1995; Pettit et al., 1994) for LTP. Based on biochemical studies it has long been proposed that CaMKII could be responsible for maintaining the long-term increase in synaptic strength. During calcium/calmodulin activation of CaMKII, the molecule undergoes autophosphorylation resulting in a constitutively active, calcium-independent enzyme (Lisman et al., 2012). The abundance of CaMKII in neurons and specifically at the PSD, as well as its unique molecular properties, made it an extremely attractive candidate for a "memory molecule". Although very attractive, recent two-photon fluorescence lifetime imaging of single spines during the induction of LTP does not support this model. It was found that CaMKII activation during pairing is transient, returning to baseline in about 1 minute (Lee et al., 2009). Therefore, whatever process maintains LTP it must be downstream of CaMKII. The critical downstream target(s) of CaMKII remain elusive, although many substrates of CaMKII have been identified including phosphorylation of the AMPAR itself (Barria et al., 1997; Mammen et al., 1997; Roche et al., 1996). Recent evidence suggests that CaMKII may trigger the local persistent activation of Rho GTPases, specifically RhoA and Cdc42, which are critical for both structural and functional plasticity (Murakoshi et al., 2011). How CaMKII activates these Rho GTPases is unclear. It is also a mystery as to how activated Rho GTPases ultimately recruit AMPARs to the synapse.

It has long been accepted that the critical, and perhaps only, role for NMDARs in plasticity is to trigger LTP by transiently elevating spine calcium. However, there is growing evidence that following NMDAR activation CaMKII is translocated to the PSD by binding to the C-tail of the GluN2B subunit and this interaction is important for LTP (Barria and Malinow, 2002; Bayer et al., 2006; Halt et al., 2012; Strack and Colbran, 1998). This model was originally tested by overexpressing a mutant GluN2B, which did not bind CaMKII, into wild type slice cultured neurons (Barria and Malinow, 2005). Neurons expressing this mutant failed to exhibit LTP. More recently a knock-in mouse was generated in which the wild type GluN2B subunit is replaced by a mutated version, which is unable to bind CaMKII (Halt et al., 2012). Although this mutation prevented the translocation of CaMKII to the synapse, LTP could still be induced, albeit at 50% of wild type. Further studies are necessary to determine the precise role that CaMKII binding to GluN2B plays in the generation of LTP.

Importance of AMPAR trafficking

There is general consensus that the dynamic but highly regulated trafficking of AMPARs to and from synapses is critical in the expression of LTP. Over the last 15 years the field of LTP has shifted towards molecular approaches to examine the basic cell biology regulating AMPAR mobility. Research has generally focused on three important areas: 1) modification of the receptor itself (phosphorylation and protein-protein interactions and their effects on trafficking); 2) the role of auxiliary subunits of AMPARs in LTP; and 3) role of PSD scaffolding proteins.

There are two general models for how the synapse acquires AMPARs during LTP. These models are not mutually exclusive. In the first model the activity dependent step is the synaptic capture of surface receptors that are freely moving via lateral diffusion into and out of the synapse (Opazo et al., 2012). One could imagine that activity increases the number of receptor binding sites or "slots" available in the PSD or that activity changes the AMPARs such that when they diffuse into the synapse they are captured. In the second model activity triggers exocytosis, inserting AMPARs into the synapse from an intracellular pool. It is proposed that the exocytosis occurs perisynaptically, in which case one still requires a means for the exocytosed receptors to be captured in the PSD.

Three approaches have been used to study postsynaptic exocytosis of AMPARs. The first approach involves imaging expressed receptors, which have been tagged on their extracellular N-terminus with a pH-sensitive superecliptic pHluorin (SEP). The SEP-tagged receptor, generally the GluA1 subunit (SEP-GluA1), is quenched in the acidic environment of the endosome, but immediately fluoresces when exposed to the extracellular environment. A caveat with these studies is that SEP-GluA1 is overexpressed and therefore could end up in compartments that normally do not contain AMPARs. With this approach a number of investigators have observed activity-dependent exocytosis of AMPARs, although there is some debate as to whether this occurs only in dendrites (Lin et al., 2009; Makino and Malinow, 2009; Yudowski et al., 2007) or additionally directly in spines (Kennedy et al., 2010; Patterson et al., 2010).

The second approach uses a photoreactive, irreversible AMPAR antagonist, ANQX. In the presence of ultraviolet light ANQX rapidly binds covalently to the receptor irreversibly silencing surface AMPARs. Following this silencing recovery of synaptic AMPARs is slow requiring many hours (Adesnik et al., 2005; Kamiya, 2012), but somatic extrasynaptic surface receptors recover in the matter of minutes (Adesnik et al., 2005). Based on the effects of ANQX on LTP, it is proposed that there is an initial delivery of AMPARs from the intracellular pool, but not at later stages (Kamiya, 2012). These findings suggest that during basal conditions the supply of AMPARs to the synapse by exocytosis is extremely slow, but that LTP can trigger a rapid and brief insertion of AMPARs from intracellular stores.

The third approach is to block exocytosis by interfering with various proteins required for membrane fusion. Although there is controversy as to the effects of blocking exocytosis on basal synaptic transmission, most studies have reported that LTP is greatly reduced. These studies have used botulinum toxin (Lledo et al., 1998; Yang et al., 2008), tetanus toxin (Asrar et al., 2009), a peptide that interferes with syntaxin 4 (Kennedy et al., 2010), and the knockdown of complexin (Ahmad et al., 2012). In most of these studies an early phase (10–25 minutes) of potentiation remains.

What might be the relative importance of the capture of surface receptors compared to the exocytosis of receptors? This has been addressed by the expression of SEP-GluA1 (Patterson et al., 2010). These authors induced LTP on a single spine with glutamate uncaging and compared the increase in spine fluorescence with and without prior bleaching of surface receptors. With prior bleaching the increase in fluorescence can be attributed entirely to exocytosis whereas without prior bleaching much of the increase will be due to clustering of preexisting surface receptors. They found that the increase in fluorescence after bleaching was a small fraction of that without prior bleaching, suggesting that spine AMPAR recruitment is largely due to the capture of preexisting surface receptors.

Are AMPARs/TARPs the direct targets of the LTP signal?

An important unanswered question remains, namely how AMPARs are recruited to the PSD. Most of the attention has focused on the phosphorylation and protein-protein interactions with the cytoplasmic C-tails of AMPARs (Bredt and Nicoll, 2003; Collingridge et al., 2004; Malinow and Malenka, 2002; Shepherd and Huganir, 2007) and their auxiliary subunits (Coombs and Cull-Candy, 2009; Jackson and Nicoll, 2011; Kato et al., 2010; Straub and Tomita, 2011). These studies emphasize the multiple ways that AMPAR trafficking can be modified. A common model of LTP is that the GluA1 C-tail is critically involved (Hayashi et al., 2000; Shepherd and Huganir, 2007; Shi et al., 2001). It has also been shown that phosphorylation can increase the single channel conduction of AMPARs (Kristensen et al., 2011) and that this may contribute to LTP (Benke et al., 1998). However, in none of these

studies has it been demonstrated that either phosphorylation or protein-protein interactions are absolutely required for LTP.

In contrast to the large literature on the direct modification of AMPARs in LTP, relatively little is known about the role of auxiliary subunits. Mice lacking TARP γ-8, which is highly expressed in the hippocampus, have a severe defect in LTP (Rouach et al., 2005). While this finding could be interpreted as a direct requirement for γ-8 in LTP, we noted that the pool of extrasynaptic AMPARs is severely depleted in these mice. More recent studies have shown that LTP requires a pool of extrasynaptic AMPARs (Granger et al., 2012) and thus the impairment in LTP in the γ-8 KO mouse is more likely due to an indirect effect. In addition, findings using a knock-in mouse expressing TARPγ-8 lacking the C-terminal PDZ ligand, supports an indirect mechanism (Sumioka et al., 2011) The C-terminal tails of TARPs have multiple phosphorylation sites (Chetkovich et al., 2002; Sumioka et al., 2010; Tomita et al., 2005). Expressing a phospho-dead stargazin construct prevented LTP in hippocampal neurons, whereas expressing phosphomimic stargazin construct blocked LTD (Tomita et al., 2005), but not clear if this is an essential element of LTP.

What domain(s) of the AMPAR are required for LTP?

To define the minimal requirements for LTP, we have used a single cell molecular replacement strategy (Granger et al., 2012). All endogenous AMPAR subunits are deleted by expressing Cre in neurons from triple floxed mice (*Gria1*$^{fl/fl}$ *Gria2*$^{fl/fl}$ *Gria3*$^{fl/fl}$) and then mutated forms of AMPAR subunits are re-introduced onto this null background. In striking contrast to the prevailing model, there was no requirement of the GluA1 C-tail for LTP. In fact, replacement with the GluA2 subunit showed normal LTP, as did an artificially expressed kainate receptor not normally found at these synapses. Although the expressed homomeric KARs are calcium permeable, the LTP was completely blocked by the NMDAR selective antagonist APV, further confirming that KARs are capable of expressing normal LTP. The lack of involvement of calcium entry through the KAR could be due either to lower calcium permeability of KARs compared to NMDARs, or to calcium microdomains. The only conditions under which LTP was impaired were those with dramatically decreased AMPA receptor surface expression, indicating a requirement for a reserve pool of receptors. These results demonstrate the synapse's remarkable flexibility to potentiate with a variety of glutamate receptor subtypes, requiring a fundamental change in our thinking with regard to the core molecular events underlying synaptic plasticity.

Conclusion

In this review we show that there are remarkably few mechanisms that are clearly "required" for LTP, with NMDAR activation being at the top of the list, followed by CaMKII. However, we are still left with a number of unanswered questions. Does CaMKII cause a change in the PSD so that the PSD can accommodate more AMPARs? If so, what is the nature of the change? Is it due to phosphorylation or might it involve a structural role of translocated CaMKII? Does CaMKII modify AMPAR/TARP complexes to facilitate synaptic capture? If so, how does this occur? If exocytosis of AMPAR-containing recycling endosomes contributes to LTP how does CaMKII initiate this process? Finally, given that the CaMKII signal is transient, what is the mechanism underlying the maintenance of LTP? To be continued…

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