

Accepted Manuscript

Long-term potentiation: peeling the onion

Roger A. Nicoll, Katherine W. Roche

PII: S0028-3908(13)00067-1

DOI: [10.1016/j.neuropharm.2013.02.010](https://doi.org/10.1016/j.neuropharm.2013.02.010)

Reference: NP 4964

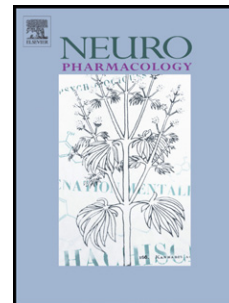
To appear in: *Neuropharmacology*

Received Date: 12 February 2013

Accepted Date: 12 February 2013

Please cite this article as: Nicoll, R.A., Roche, K.W., Long-term potentiation: peeling the onion, *Neuropharmacology* (2013), doi: 10.1016/j.neuropharm.2013.02.010.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Long-term potentiation: peeling the onion

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.

Long-term potentiation: peeling the onion.

Roger A. Nicoll^{1*} and Katherine W. Roche²

¹ Departments of Cellular and Molecular Pharmacology and Physiology, University of California, San Francisco, CA 94143.

²Receptor Biology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892.

* To whom correspondence may be addressed: Roger Nicoll, Department of Cellular and Molecular Pharmacology, University of California, San Francisco, Genentech Hall, 600 16th Street, Box 2140, San Francisco, CA 94143-2140, Tel : (415) 476-2018, Email: roger.nicoll@ucsf.edu

Introduction

One of the most remarkable features of the brain is its 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 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 supercliptic 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

AMPA 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 TARP γ -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 phospho-mimic 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...

References

- Abbas, A. K., Dozmorov, M., Li, R., Huang, F. S., Hellberg, F., Danielson, J., Tian, Y., Ekstrom, J., Sandberg, M., Wigstrom, H., 2009. Persistent LTP without triggered protein synthesis. *Neurosci Res* 63, 59-65.
- Adesnik, H., Nicoll, R. A., England, P. M., 2005. Photoinactivation of native AMPA receptors reveals their real-time trafficking. *Neuron* 48, 977-985.
- Ahmad, M., Polepalli, J. S., Goswami, D., Yang, X., Kaeser-Woo, Y. J., Sudhof, T. C., Malenka, R. C., 2012. Postsynaptic complexin controls AMPA receptor exocytosis during LTP. *Neuron* 73, 260-267.
- Asrar, S., Zhou, Z., Ren, W., Jia, Z., 2009. Ca(2+) permeable AMPA receptor induced long-term potentiation requires PI3/MAP kinases but not Ca/CaM-dependent kinase II. *PLoS ONE* 4, e4339.
- Barria, A., Derkach, V., Soderling, T., 1997. Identification of the Ca²⁺/calmodulin-dependent protein kinase II regulatory phosphorylation site in the alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate-type glutamate receptor. *J Biol Chem* 272, 32727-32730.
- Barria, A., Malinow, R., 2002. Subunit-specific NMDA receptor trafficking to synapses. *Neuron* 35, 345-353.
- Barria, A., Malinow, R., 2005. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. *Neuron* 48, 289-301.
- Bayer, K. U., LeBel, E., McDonald, G. L., O'Leary, H., Schulman, H., De Koninck, P., 2006. Transition from reversible to persistent binding of CaMKII to postsynaptic sites and NR2B. *J Neurosci* 26, 1164-1174.
- Bekkers, J. M., Stevens, C. F., 1990. Presynaptic mechanism for long-term potentiation in the hippocampus. *Nature* 346, 724-729.
- Benke, T. A., Luthi, A., Isaac, J. T., Collingridge, G. L., 1998. Modulation of AMPA receptor unitary conductance by synaptic activity. *Nature* 393, 793-797.
- Bliss, T. V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 232, 331-356.
- Bredt, D. S., Nicoll, R. A., 2003. AMPA receptor trafficking at excitatory synapses. *Neuron* 40, 361-379.
- Chetkovich, D. M., Chen, L., Stocker, T. J., Nicoll, R. A., Bredt, D. S., 2002. Phosphorylation of the postsynaptic density-95 (PSD-95)/discs large/zona occludens-1 binding site of stargazin regulates binding to PSD-95 and synaptic targeting of AMPA receptors. *J Neurosci* 22, 5791-5796.

- Collingridge, G. L., Isaac, J. T., Wang, Y. T., 2004. Receptor trafficking and synaptic plasticity. *Nat Rev Neurosci* 5, 952-962.
- Collingridge, G. L., Kehl, S. J., McLennan, H., 1983. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J Physiol* 334, 33-46.
- Coombs, I. D., Cull-Candy, S. G., 2009. Transmembrane AMPA receptor regulatory proteins and AMPA receptor function in the cerebellum. *Neuroscience* 162, 656-665.
- Del Castillo, J., Katz, B., 1954. Quantal components of the end-plate potential. *J Physiol* 124, 560-573.
- Giese, K. P., Fedorov, N. B., Filipkowski, R. K., Silva, A. J., 1998. Autophosphorylation at Thr286 of the alpha calcium-calmodulin kinase II in LTP and learning. *Science* 279, 870-873.
- Granger, A. J., Shi, Y., Lu, W., Cerpas, M., Nicoll, R. A., 2012. LTP requires a reserve pool of glutamate receptors independent of subunit type. *Nature* (in press).
- Halt, A. R., Dallapiazza, R. F., Zhou, Y., Stein, I. S., Qian, H., Juntti, S., Wojcik, S., Brose, N., Silva, A. J., Hell, J. W., 2012. CaMKII binding to GluN2B is critical during memory consolidation. *EMBO J* 31, 1203-1216.
- Harvey, C. D., Svoboda, K., 2007. Locally dynamic synaptic learning rules in pyramidal neuron dendrites. *Nature* 450, 1195-1200.
- Hayashi, Y., Shi, S. H., Esteban, J. A., Piccini, A., Poncer, J. C., Malinow, R., 2000. Driving AMPA receptors into synapses by LTP and CaMKII: requirement for GluR1 and PDZ domain interaction. *Science* 287, 2262-2267.
- Isaac, J. T., Nicoll, R. A., Malenka, R. C., 1995. Evidence for silent synapses: implications for the expression of LTP. *Neuron* 15, 427-434.
- Jackson, A. C., Nicoll, R. A., 2011. The expanding social network of ionotropic glutamate receptors: TARPs and other transmembrane auxiliary subunits. *Neuron* 70, 178-199.
- Johnstone, V. P., Raymond, C. R., 2011. A protein synthesis and nitric oxide-dependent presynaptic enhancement in persistent forms of long-term potentiation. *Learn Mem* 18, 625-633.
- Kamiya, H., 2012. Photochemical inactivation analysis of temporal dynamics of postsynaptic native AMPA receptors in hippocampal slices. *J Neurosci* 32, 6517-6524.
- Kato, A. S., Gill, M. B., Yu, H., Nisenbaum, E. S., Brecht, D. S., 2010. TARPs differentially decorate AMPA receptors to specify neuropharmacology. *Trends Neurosci* 33, 241-248.
- Kennedy, M. J., Davison, I. G., Robinson, C. G., Ehlers, M. D., 2010. Syntaxin-4 defines a domain for activity-dependent exocytosis in dendritic spines. *Cell* 141, 524-535.
- Kristensen, A. S., Jenkins, M. A., Banke, T. G., Schousboe, A., Makino, Y., Johnson, R. C., Huganir, R., Traynelis, S. F., 2011. Mechanism of Ca²⁺/calmodulin-dependent kinase II regulation of AMPA receptor gating. *Nat Neurosci* 14, 727-735.
- Lee, S. J., Escobedo-Lozoya, Y., Szatmari, E. M., Yasuda, R., 2009. Activation of CaMKII in single dendritic spines during long-term potentiation. *Nature* 458, 299-304.
- Liao, D., Hessler, N. A., Malinow, R., 1995. Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature* 375, 400-404.

- Lin, D. T., Makino, Y., Sharma, K., Hayashi, T., Neve, R., Takamiya, K., Huganir, R. L., 2009. Regulation of AMPA receptor extrasynaptic insertion by 4.1N, phosphorylation and palmitoylation. *Nat Neurosci* 12, 879-887.
- Lisman, J., Yasuda, R., Raghavachari, S., 2012. Mechanisms of CaMKII action in long-term potentiation. *Nat Rev Neurosci* 13, 169-182.
- Lledo, P. M., Hjelmstad, G. O., Mukherji, S., Soderling, T. R., Malenka, R. C., Nicoll, R. A., 1995. Calcium/calmodulin-dependent kinase II and long-term potentiation enhance synaptic transmission by the same mechanism. *Proc Natl Acad Sci U S A* 92, 11175-11179.
- Lledo, P. M., Zhang, X., Südhof, T. C., Malenka, R. C., Nicoll, R. A., 1998. Postsynaptic membrane fusion and long-term potentiation. *Science* 279, 399-403.
- Lomo, T., 1966. Frequency potentiation of excitatory synaptic activity in the dentate area of the hippocampal formation. *Acta Physiol. Scand.* 68, 128.
- Makino, H., Malinow, R., 2009. AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Neuron* 64, 381-390.
- Malinow, R., Malenka, R. C., 2002. AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* 25, 103-126.
- Malinow, R., Tsien, R. W., 1990. Presynaptic enhancement shown by whole-cell recordings of long-term potentiation in hippocampal slices. *Nature* 346, 177-180.
- Mammen, A. L., Kameyama, K., Roche, K. W., Huganir, R. L., 1997. Phosphorylation of the alpha-amino-3-hydroxy-5-methylisoxazole4-propionic acid receptor GluR1 subunit by calcium/calmodulin-dependent kinase II. *J Biol Chem* 272, 32528-32533.
- Matsuzaki, M., Honkura, N., Ellis-Davies, G. C., Kasai, H., 2004. Structural basis of long-term potentiation in single dendritic spines. *Nature* 429, 761-766.
- Murakoshi, H., Wang, H., Yasuda, R., 2011. Local, persistent activation of Rho GTPases during plasticity of single dendritic spines. *Nature* 472, 100-104.
- Nicoll, R. A., 2003. Expression mechanisms underlying long-term potentiation: a postsynaptic view. *Philos Trans R Soc Lond B Biol Sci* 358, 721-726.
- Nicoll, R. A., Malenka, R. C., 1995. Contrasting properties of two forms of long-term potentiation in the hippocampus. *Nature* 377, 115-118.
- Nicoll, R. A., Malenka, R. C., 1999. Expression mechanisms underlying NMDA receptor-dependent long-term potentiation. *Annals of the New York Academy of Sciences* 868, 515-525.
- Nicoll, R. A., Schmitz, D., 2005. Synaptic plasticity at hippocampal mossy fibre synapses. *Nat Rev Neurosci* 6, 863-876.
- Opazo, P., Sainlos, M., Choquet, D., 2012. Regulation of AMPA receptor surface diffusion by PSD-95 slots. *Curr Opin Neurobiol* 22, 453-460.
- Patterson, M. A., Szatmari, E. M., Yasuda, R., 2010. AMPA receptors are exocytosed in stimulated spines and adjacent dendrites in a Ras-ERK-dependent manner during long-term potentiation. *Proc Natl Acad Sci U S A* 107, 15951-15956.
- Pettit, D. L., Perlman, S., Malinow, R., 1994. Potentiated transmission and prevention of further LTP by increased CaMKII activity in postsynaptic hippocampal slice neurons. *Science* 266, 1881-1885.
- Reymann, K. G., Frey, J. U., 2007. The late maintenance of hippocampal LTP: requirements, phases, 'synaptic tagging', 'late-associativity' and implications. *Neuropharmacology* 52, 24-40.

- Roche, K. W., O'Brien, R. J., Mammen, A. L., Bernhardt, J., Huganir, R. L., 1996. Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. *Neuron* 16, 1179-1188.
- Rouach, N., Byrd, K., Petralia, R. S., Elias, G. M., Adesnik, H., Tomita, S., Karimzadegan, S., Kealey, C., Bredt, D. S., Nicoll, R. A., 2005. TARP gamma-8 controls hippocampal AMPA receptor number, distribution and synaptic plasticity. *Nat Neurosci* 8, 1525-1533.
- Sanes, J. R., Lichtman, J. W., 1999. Can molecules explain long-term potentiation? *Nat Neurosci* 2, 597-604.
- Schuman, E. M., Dynes, J. L., Steward, O., 2006. Synaptic regulation of translation of dendritic mRNAs. *J Neurosci* 26, 7143-7146.
- Schwartzkroin, P. A., Wester, K., 1975. Long-lasting facilitation of a synaptic potential following tetanization in the in vitro hippocampal slice. *Brain Res* 89, 107-119.
- Shepherd, J. D., Huganir, R. L., 2007. The cell biology of synaptic plasticity: AMPA receptor trafficking. *Annu Rev Cell Dev Biol* 23, 613-643.
- Shi, S., Hayashi, Y., Esteban, J. A., Malinow, R., 2001. Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. *Cell* 105, 331-343.
- Strack, S., Colbran, R. J., 1998. Autophosphorylation-dependent targeting of calcium/calmodulin-dependent protein kinase II by the NR2B subunit of the N-methyl- D-aspartate receptor. *J Biol Chem* 273, 20689-20692.
- Straub, C., Tomita, S., 2011. The regulation of glutamate receptor trafficking and function by TARPs and other transmembrane auxiliary subunits. *Curr Opin Neurobiol* 22, 488-495.
- Sumioka, A., Brown, T. E., Kato, A. S., Bredt, D. S., Kauer, J. A., Tomita, S., 2011. PDZ binding of TARPgamma-8 controls synaptic transmission but not synaptic plasticity. *Nat Neurosci* 14, 1410-1412.
- Sumioka, A., Yan, D., Tomita, S., 2010. TARP phosphorylation regulates synaptic AMPA receptors through lipid bilayers. *Neuron* 66, 755-767.
- Tomita, S., Stein, V., Stocker, T. J., Nicoll, R. A., Bredt, D. S., 2005. Bidirectional synaptic plasticity regulated by phosphorylation of stargazin-like TARPs. *Neuron* 45, 269-277.
- Villers, A., Godaux, E., Ris, L., 2012. Long-lasting LTP requires neither repeated trains for its induction nor protein synthesis for its development. *PLoS ONE* 7, e40823.
- Yang, Y., Wang, X. B., Frerking, M., Zhou, Q., 2008. Delivery of AMPA receptors to perisynaptic sites precedes the full expression of long-term potentiation. *Proc Natl Acad Sci U S A* 105, 11388-11393.
- Yudowski, G. A., Puthenveedu, M. A., Leonoudakis, D., Panicker, S., Thorn, K. S., Beattie, E. C., von Zastrow, M., 2007. Real-time imaging of discrete exocytic events mediating surface delivery of AMPA receptors. *J Neurosci* 27, 11112-11121.

No highlights supplied

ACCEPTED MANUSCRIPT