COMMENTARY

J. David Sweatt

Division of Neuroscience
Baylor College of Medicine
Houston, Texas 77030 USA

Toward a Molecular Explanation for Long-Term Potentiation

Introduction

The molecular mechanisms for long-term potentiation (LTP) may seem hopelessly complex, and no doubt the lack of clarity and concision of the immense LTP literature is a source of frustration for many (Sanes and Lichtman 1999). However, being inherently optimistic it seems to me that certain generalizations are beginning to emerge that allow an initial formulation of a molecular explanation for LTP. At this point in time we do not have in hand all the puzzle pieces concerning the molecular basis for LTP, so any explanation is by necessity incomplete and likely to contain some errors. Nevertheless, I feel it is constructive to present a working draft of a molecular model for one specific type of LTP, in the hope that it will present a useful framework for further discussion and experimentation.

In this commentary I will describe several criteria that I use to narrow down the enormous LTP literature, and define certain terms commonly used and misused in the LTP literature so that we have a common vocabulary. I propose a set of criteria for inclusion of a given signal transduction cascade into a “core” mechanism for LTP and present an initial model of such a mechanism for one type of LTP. Finally, I will comment on the complexity of the molecular mechanisms of LTP induction, maintenance, and expression and point out a few emerging themes for the biochemistry of LTP. The latter serves to help manage the complexity of LTP biochemistry by generating functional categories for the molecules of LTP.

What LTP Are We Talking About?

There are many different types of LTP in the mammalian CNS—hippocampal, cortical, cerebellar, NMDA receptor-dependent and independent—just to name a few prominent categories. Therefore, we need to specify, to the best extent possible, exactly which LTP we are discussing. In this commentary I will be discussing NMDA receptor-dependent LTP at Schaffer collateral/commissural synapses in area CA1 of rat or mouse hippocampus, in most cases induced using multiple, spaced trains of 1 sec/100 Hz stimuli. I choose this subtype of LTP because it has the widest variety of direct biochemical data available.

What Aspect of LTP Are We Talking About?

LTP, as originally defined by Bliss and Lomo (1973), is manifest as two physiologic components. The first component, which has received by far the most attention, is an increase in synaptic strength. This is typically measured as an increase in the initial slope of the EPSP (or EPSP magnitude). This effect is subserved by an increase in neurotransmitter release, an increase in postsynaptic receptor number or efficacy, or both. Although the locus of LTP expression (pre- vs. postsynaptic) has been widely debated and is a source of continuing controversy, my reading of the literature leads me to conclude that there is a convincing case that postsynaptic changes in AMPA receptor function contribute to the

expression of LTP. My model will incorporate mechanisms to achieve this effect. The physiologic evidence for changes in neurotransmitter release is less convincing to me, but there is convincing biochemical evidence that presynaptic changes do occur in LTP. Thus my model will contain a mechanism to account for lasting changes in both the pre- and postsynaptic compartments.

A second component of LTP discovered by Bliss and Lomo (1973) is referred to as EPSP-slope (E-S) potentiation, which is a term used to refer to the postsynaptic cell having an increased probability of firing an action potential at a constant strength of synaptic input. While E-S potentiation was originally explained based on alterations in recurrent inhibitory connections in area CA1, more recent work has suggested that E-S potentiation is a manifestation of increased excitability in the postsynaptic neuron. My model will incorporate a molecular mechanism to account for this aspect of LTP.

Finally, I should note in passing that emerging evidence suggests that morphological changes are likely to occur in LTP. I will not try to explicitly address a molecular basis for this effect as the mechanisms underlying these types of morphological changes are ill-defined at present. However, many of the molecules already implicated in LTP, such as cytoskeletal proteins, cell-adhesion molecules, and postsynaptic scaffolding proteins, are likely to be involved in subserving these types of changes. I similarly will duck the important issue of the basis of control of local protein synthesis at synapses, based on a dearth of information concerning the signal transduction mechanisms operating to control this process in LTP. In the future it will likely be necessary that any model for LTP will have to incorporate mechanisms for both local protein synthesis and morphological changes.

What Types of Mechanisms Are Involved in LTP Biochemistry?

I would like to point out three terms widely used and abused in the LTP literature, so that we can use a common nomenclature in discussing the molecular mechanisms of LTP. *Induction* refers to the transient events serving to trigger the formation of LTP. A *maintenance* mechanism refers to the persisting biochemical signal that lasts in the cell. This persisting biochemical signal acts upon an effector, for example a glutamate receptor, resulting in the *expression* of LTP. It is important to keep in mind that these processes can be differentially inhibited, as was beautifully illustrated in an early experiment by Malinow, Madison, and Tsien (1988). Imagine that you apply an enzyme inhibitor before, during, and after the period of LTP-inducing, high-frequency stimulation and find that the inhibitor blocks LTP. You could not distinguish whether the inhibited enzyme is required for the induction, the expression, or the maintenance of LTP. To distinguish among these possibilities, imagine instead applying the inhibitor selectively at different time points in the experiment. If you apply the inhibitor only during the tetanus and it blocks LTP you can conclude that the enzyme is necessary for LTP induction. If you apply the inhibitor after the tetanus and it reverses the potentiation it may be blocking either the maintenance or expression of LTP. To illustrate this, imagine that the mechanism of LTP maintenance and expression is an autonomously active protein kinase phosphorylating an AMPA receptor (Barria et al. 1997). In this case transient application of a kinase inhibitor would reversibly block LTP by blocking the capacity of

the kinase to phosphorylate the receptor, but the potentiation will recover after removal of the inhibitor because the kinase is still autonomously active (Malinow et al. 1988). This is a blockade of LTP *expression*. However, if the kinase inhibitor causes the kinase to return to its basal state the potentiation will not recover, and the inhibitor has blocked the *maintenance* of LTP.

What Phase of LTP Are We Talking About?

Contemporary models divide long-lasting LTP into three phases. LTP comprising all three phases is induced with repeated trains of high-frequency stimulation in area CA1, and the phases are expressed sequentially over time to constitute what we call LTP. Late LTP (L-LTP) is dependent for its induction on changes in gene expression and lasts many hours. Early LTP (E-LTP) is subserved by persistently activated protein kinases and starts at around 30 min or less and is over by ~2–3 hr. The first stage of LTP, generally referred to as short-term potentiation, is independent of protein kinase activity for its induction or expression and lasts ~30–45 min¹. I prefer to refer to the first stage of LTP as initial LTP to emphasize that it is a persistent form of NMDA receptor-dependent synaptic plasticity that is induced by LTP-inducing tetanic stimulation and is a prelude to E-LTP and L-LTP (Roberson et al. 1996). The biochemical mechanisms for initial-LTP induction, maintenance, and expression are completely mysterious at this time. The mechanisms for E-LTP and L-LTP are the subject of the remainder of this commentary².

It is important for the reader to synthesize the two preceding paragraphs. Simply stated, three phases of LTP (Initial-, E-, and L-LTP) times three distinct underlying mechanisms for each phase (induction, maintenance, and expression) gives nine separate categories into which any particular molecular mechanism contributing to LTP may fit (see Table 1).

What Are the Core Mechanisms for LTP?

Before proposing a specific set of core mechanisms for LTP, I would like to review some fundamental principles; while the specifics are likely to change, the fundamentals can serve as a lasting guide in evaluating new information. I will review several experimental criteria that I think serve as useful guidelines in deciding if a particular molecular mechanism should be promoted to “core” status. All the criteria are general principles of hypothesis testing and will be quite remedial for most readers; thus, one might argue that there is no need to present them. On the other

¹Readers may note the ambiguity in the times specified for each phase of LTP. For technical reasons most L-LTP experiments are performed at room temperature or 27–28°C. Many E-LTP experiments, especially those involving direct biochemical measurements, are performed at 32–35°C. Given the pronounced temperature dependence of essentially all chemical reactions (a doubling of reaction rate for a change from room temperature to 32°C is fairly common for biochemical reactions), it is difficult to try to compare one set of conditions to the other. Late LTP may start at 3 hr at room temperature, start at 1.5 hr at 32°C, and start at 45 min *in vivo*.

²An additional phase of LTP, intermediate-LTP, has also been proposed (Winder et al. 1998). At this time I am not incorporating this phase of LTP into my model because intermediate LTP might be explained as a prolonged form of E-LTP. In addition, intermediate LTP was defined based on manipulations in phosphatase activity that are likely to affect LTP induction mechanisms. I propose that new phases of LTP be defined based on differences in maintenance mechanisms.

Table 1: *Phases and mechanisms of LTP*

Phase	Trigger	Mechanism		
		induction	maintenance	expression
Initial-LTP	NMDA receptor	?	?	?
E-LTP	NMDA receptor	KI ^a CaMKII activation; PKC activation; partially PKA activation; partially MAPK activation	KI autonomously active CaMKII and PKC	KI AMPA receptor phosphorylation; K channel phosphorylation?
L-LTP	NMDA receptor	altered gene expression by MAPK and PKA, CREB phosphorylation; synaptic tagging?	half-life of mRNA and protein? prolonged changes in expression or synthesis?	Increased AMPA receptors postsynaptically; altered K channel expression?

^a(KI) Kinase independent.

hand, one need only pick up any randomly selected LTP paper to see why their reiteration is useful—they emphasize that hypothesis testing is a process wherein multiple, independent lines of evidence are needed to support any one hypothesis. Experimental manipulations of any single sort, which can of necessity test only a single prediction of a hypothesis, are insufficient to consider a hypothesis well supported.

CRITERION 1— REPRODUCIBILITY

This criterion is so obvious that I will not belabor it. I list it only for the sake of completeness, and as a contrived means of being able to inject some editorial comments into my commentary. As has been emphasized (Sanes and Lichtman 1999) the *Nature* of modern *Science* is such that publication of any single finding in a high-profile journal does not necessarily imply any assurance of reproducibility. In fact, the more cynical would likely assert that journal impact factor has tended to correlate negatively with reproducibility, at least as far as the LTP literature goes. The LTP literature is replete with nonreproducible and quasireproducible (i.e., reproducible within a single lab) results. What is the take-home message? *Caveat emptor*.

Review writers and commentators should make a good-faith effort to assess the reproducibility of the data implicating any single molecule in LTP before promulgating it as a candidate component of LTP biochemistry. Newcomers to the field should scour the literature to assess the reproducibility of any particular finding before attempting to follow it up experimentally, keeping in mind that the data refuting any high-profile finding is likely buried in a more obscure journal.

Returning to the main line of our discussion, the following three criteria are specific types of experimental manipulations that are used to test the predictions of hypotheses. No single one or combination of any two can stand on their own. However, if all three criteria are met a very compelling case has been made and the hypothesis can be considered rigorously tested. I propose that the following three criteria, in conjunction with the reproducibility criterion above, be met before any molecule (or molecular cascade) is included as part of the “core” mechanism for LTP.

CRITERION 2—BLOCKING
THE ACTIVITY OF THE
MOLECULE BLOCKS
LTP INDUCTION

This typically is accomplished using pharmacologic inhibition or genetic manipulation and, by far, is the predominant category of experiments implicating molecules in LTP. Assuming perfect specificity of the experimental manipulation it is still important to keep in mind that an inhibitor can act by affecting any of the mechanisms highlighted in Table 1, that is, the manipulation may block induction, maintenance, or expression. In addition, it is possible for a molecule or its activity to be necessary for LTP because it subserves some obligatory baseline function, but yet the molecule may have no direct involvement in any *signal transduction* cascade necessary for LTP. For example, assume that NMDA receptors are constitutively phosphorylated by some protein kinase and that this phosphorylation event is necessary for the NMDA receptor to be functional. Removing the kinase would by definition block any form of NMDA receptor-dependent LTP, but the kinase itself would play no role as a downstream effector involved in LTP induction, maintenance, or expression.

CRITERION 3—DIRECTLY
ACTIVATING THE MOLECULE
SHOULD PRODUCE EITHER
LTP OR SYNAPTIC
POTENTIATION

This experiment is most straightforward in the context of mechanisms for LTP maintenance, where application of the activated form of the molecule should be capable of producing synaptic potentiation. Similarly, if a molecule is involved in LTP induction and that pathway is sufficient to elicit LTP (or a phase thereof), application of the molecule should produce LTP. This experiment is more problematic in a situation where the molecule may be necessary, but not sufficient, for LTP induction; in this case application of the molecule will not produce LTP. However, even in this case concomitant application of the molecule along with the additional necessary factors should be capable of producing LTP. The mirror image of this caveat is not often considered; what if a molecule is sufficient but not necessary for LTP induction? Or if the molecule plays a necessary role in LTP induction but by an entirely different mechanism is capable of producing LTP when strongly or aberrantly activated? The more we learn about the multitude of sites and mechanisms for plasticity at hippocampal synapses, the greater our realization of the potential for this situation to occur (see, e.g., Mammen et al. 1997).

CRITERION 4—THE
MOLECULE SHOULD BE
ACTIVATED (OR ELEVATED)
WITH LTP-INDUCING
STIMULATION

This is one of the classic criteria among biochemistry types for implicating a molecule in a signal transduction cascade, arising from the experimental traditions of Earl Sutherland and his coworkers in discovering the cAMP cascade. However, this type of experiment has not been as popular in the electrophysiologist-dominated LTP field. This is partly due, in my opinion, to technical considerations and partly due to the correlative nature of the data obtained using this approach.

Nevertheless, data of this sort in combination with pharmacologic/genetic data addressing the necessity and sufficiency of a molecule for LTP (criteria 2 and 3) allow a compelling case to be made for a role for a given molecule in LTP.

Ideally for any molecule or signal transduction cascade to be promoted to core status for LTP induction, maintenance, or expression, each of the four criteria above must be fulfilled. This is a stringent vetting procedure and I hope that the criteria will be useful in the future as a checklist in evaluating candidate molecules. However, are there candidate signal transduction pathways than can pass this test right now? In my opinion, a convincing case can be made for four pathways at present; the PKA cascade, the MAPK (ERK) cascade, CaMKII, and PKC. As space constraints do not allow a review of the extensive literature relevant to the roles of these pathways in LTP, I have briefly summarized the relevant findings and given selected references in Table 2.

A Core Signal Transduction Cascade for LTP

The proposed core signal transduction cascade for LTP is presented graphically in Figure 1. Though a static diagram is presented, it should be kept in mind that the effects described can be divided into three broad temporal categories:

Table 2: *Signal transduction pathways*

Cascade	Phase	Induction (I) or maintenance/ expression (M/E)	Inhibitors block?	Activators mimic?	Demonstrated to occur?
CaMKII	E-LTP	I	yes (1,2)	yes (3)	yes (1,4)
		M/E	yes (when PKC inhib, 5,6)	yes (7)	yes (1,4,8)
	L-LTP	I	?	?	yes (1,4,8)
		M/E	?	?	no (8)
PKC	E-LTP	I	yes (5,9–11)	yes? (3,12–15)	yes (16–19)
		M/E	yes (when CaMKII inhib, 6,11)	yes (12–15)	yes (16–19)
	L-LTP	I	partially (20–23)	?	yes (16–19)
		M/E	?	?	no (16–19)
PKA	E-LTP	I	yes, indirectly. (24–26)	no (27)	yes (28–30)
		M/E	no (30)	yes (31,32)	no (30)
	L-LTP	I	yes (26,27)	yes (27)	yes (28–30)
		M/E	no (32,33)	?	no (30)
MAPK	E-LTP	I	partially (34–36)	?	yes (34,37)
		M/E	no (34)	?	no (34)
	L-LTP	I	yes (34–36)	yes (27,36,38)	yes (34,37)
		M/E	no (34,36)	?	no (34)

References: (1) Barria et al. (1997); (2) Silva et al. (1992); (3) Pettit et al. (1994); (4) Ouyang et al. (1997); (5) Malinow et al. (1989); (6) Wang and Feng (1992); (7) Wang and Kelly (1995); (8) Fukunaga et al. (1993); (9) Hvalby et al. (1994); (10) Lovinger et al. (1987); (11) Colley et al. (1990); (12) Malenka et al. (1986); (13) Malenka et al. (1987); (14) Hvalby et al. (1988); (15) Hu et al., (1987); (16) Klann et al. (1991); (17) Klann et al. (1993); (18) Sacktor et al. (1993); (19) Leahy et al. (1993); (20) Matthies et al. (1991); (21) Matthies and Reymann (1993); (22) Reymann et al. (1988a); (23) Reymann et al. (1988b); (24) Winder et al. (1998); (25) Blitzler et al. (1998); (26) Blitzler et al. (1995); (27) Frey et al. (1993); (28) Chetkovich et al. (1991); (29) Chetkovich and Sweatt (1993); (30) Roberson and Sweatt (1996); (31) Chavez-Noriega and Stevens (1992); (32) Pockett et al. (1993); (33) E.D. Roberson and J.D. Sweatt, unpubl.; (34) English and Sweatt (1997); (35) Atkins et al. (1998); (36) Impey et al. (1998); (37) English and Sweatt (1996); (38) Roberson et al. (1999).

constant. This issue was also dealt with in a previously published paper (Roberson et al. 1996).

Modulators of LTP Induction

The molecules listed in Table 2 and Figure 1 are but a fraction of the numerous species that have been implicated in LTP. What place do these other molecules have in a scheme for LTP? I categorize many of these molecules as modulators of LTP induction (see Table 3 for various examples). Many molecules implicated in LTP are extrinsic factors, such as modulatory neurotransmitters, that likely alter the magnitude or probability of induction of LTP by impinging on the signal transduction pathways of the core pathway. In my estimation dopamine receptors, β -adrenergic receptors, and acetylcholine receptors fit into this category. Another category is intrinsic factors that are activated concomitantly with the core signal transduction pathway and that tend to promote LTP induction, but that are not required for LTP induction in all circumstances. The prototype for this category is nitric oxide (NO) synthase; I also place postsynaptic metabotropic glutamate receptors in this category. It is important to note that the effects of all the modulators of LTP induction are likely to be more or less pronounced depending on induction parameters such as stimulus strength, temperature, and physiologic stimulation protocol.

Components of the Synaptic Infrastructure

Another category of molecule necessary for LTP induction is molecules whose presence or function are necessary for normal operation of the synapse (Table 3 also lists examples for this category). Presynaptic calcium channels, the molecules intrinsic to mediating calcium-induced vesicle fusion, AMPA and NMDA receptors, and postsynaptic scaffolding proteins all can be included in this category. It is important to bear in mind that these same molecules are likely to be effectors of the processes that maintain LTP or modulate LTP induction.

Finally an additional subcategory of molecules are those that are normally basally active and help maintain the synaptic infrastructure. A nice example of this category is BDNF, its receptor and effectors, which have been proposed to be constitutively active at the synapse and are necessary for a normal presynaptic response to high frequency tetanic stimulation (Figurov et al. 1996; Patterson et al. 1996; Korte et al. 1998; Pozzo-Miller et al. 1999).

The Molecular Complexity of LTP Induction: A Refutation of Occam's Razor

The law of parsimony, commonly known as Occam's Razor, states that when choosing among competing hypotheses to explain a phenomenon, choose the simplest that is compatible with the existing data. This principle was formulated by William of Occam in ~1300 AD and has served science well in the 700 years since. In 1988 John Lisman formulated a parsimonious model for LTP that was consistent with available data and was completely adequate to explain LTP; generation of an autonomously active, self-regenerating CaMKII that increased synaptic strength (Lisman and Goldring 1988). In light of data obtained since 1988 the model has, to borrow one of Lisman's phrases, "turned to mush."³ It

³In a striking example of intellectual integrity, John Lisman has been one of the leading experimentalists in refuting his own well-known model (Otmakov et al. 1997). For the sake of historical accuracy, I should also point out that he was actually referring to a presentation of my data from my laboratory on the role of NO synthase in LTP (Chetkovich et al. 1993).

Table 3: *Modulators of LTP induction*

	Molecule/ cascade	Potential mechanism of action	Selected references
Modulators of LTP	DA receptors	amplification of cAMP and MAPK signal	1,2
	β -adrenergic receptors	amplification of cAMP and MAPK signal	3
	metabotropic GluR	amplification of PKC and MAPK signal	4,5
	Ube3A ubiquitin ligase	proteolytic turnover of an unknown protein	6
	NO synthase	guanylyl cyclase, PKC, NMDA receptor	7–9
Components of the Synaptic Infrastructure	BDNF	ability of release machinery to track HFS	10–13
	AMPA receptor	normal synaptic transmission	14
	NMDA receptor	normal postsynaptic response to HFS	15
	src	appropriate postsynaptic response to HFS	16
	release machinery	normal synaptic transmission	17
	PSD-95	appropriate postsynaptic response to HFS	18
	Ca ²⁺ channels	normal calcium influx with HFS	19
	potassium channels	normal electrical responses to depolarization	20
	cell adhesion molecules	stabilization of synaptic structure	21

(1) Frey et al. (1991); (2) Otmakhov and Lisman (1996); (3) Thomas et al. (1996); (4) Aiba et al. (1994); (5) Balschun et al. (1999); (6) Jiang et al. (1998); (7) Chetkovich et al. (1993); (8) Haley et al. (1993); (9) Williams et al. (1993); (10) Pozzo-Miller et al. (1999); (11); Korte et al. (1998); (12) Figurov et al. (1996); (13) Patterson et al. (1996); (14) Zamanillo et al. (1999); (15) Tsien et al. (1996); (16) Lu et al. (1998); (17) Takahashi et al. (1999); (18) Migaud et al. (1998); (19) Cavus and Teyler (1996); (20) Linden (1999); (21) Tang et al. (1998).

is now clear that no single process is likely to explain LTP or even a single phase of it. Even the relatively complicated core model presented in Figure 1 is an oversimplification, as it covers only a fraction of the processes reliably implicated in LTP induction. Occam's Razor has seemingly been overwhelmed.

How can one bring some sense of order to the immense complexity of interacting signal transduction cascades that are involved in LTP induction? Unfortunately a complete review of all the interacting molecular cascades involved in LTP induction is beyond the scope of this commentary, so I leave that to a future effort. Nevertheless, I believe that it is constructive at this point to present a brief overview of several themes that have emerged from analyzing the molecular cascades that are involved in LTP. These themes serve to provide a set of categories in which to place molecular events that have already been implicated in LTP induction, maintenance, and expression, and a context in which to place future discoveries. These broad themes are also of use because they allow one to infer certain functional consequences of the ways in which the biochemistry of LTP operates.

Theme One—Signal Amplification

Pronounced signal amplification is perhaps the most striking attribute of LTP biochemistry that has emerged. Many of the individual component processes that have been implicated in LTP induction serve to produce a highly amplified final outcome from the core LTP induction processes shown in Figure 1. Three subcategories of signal amplification mechanisms have emerged thus far: I refer to them as serial amplification, feedback amplification, and cross-talk amplification. I will provide a few specific examples for illustrative purposes.

SERIAL AMPLIFICATION

The MAP kinase cascade, with its serially linked chain of one kinase catalytically activating a downstream kinase that catalytically activates yet another kinase, is the prototype of a highly amplified signal transduction cascade. A catalytic chain reaction of this sort is capable of tremendous signal amplification (Ferrell and Machleder 1998).

FEEDBACK AMPLIFICATION

I use feedback amplification as a term to describe biochemical mechanisms that allow postsynaptic Ca^{2+} influx or membrane depolarization to augment themselves in a positive-feedback fashion. In Figure 1 a few specific examples of feedback signal amplification mechanisms in LTP induction are indicated with dashed arrows. These arrows describe the capacity of PKA to enhance voltage-gated Ca^{2+} channel function, attenuate voltage-dependent K channel function, and enhance AMPA receptor function. By these mechanisms an initial NMDA receptor-dependent influx of Ca^{2+} can amplify itself (via activation of the PKA cascade) through secondarily augmenting AMPA receptor-dependent membrane depolarization (Roche et al. 1996) and through promoting influx of additional Ca^{2+} through voltage-dependent Ca^{2+} channels (Chetkovich et al. 1991).

CROSSTALK AMPLIFICATION

I use this term to describe the capacity of one signal transduction cascade to amplify another signal transduction cascade. This is exemplified in Figure 1 by PKA activating through phosphorylation the protein

phosphatase inhibitor Inhibitor-1. By this mechanism of phosphatase inhibition PKA can amplify not only phosphorylation of its own substrates but also the level of phosphorylation of the substrates of other kinases such as CaMKII and PKC (Blitzer et al. 1995, 1998; Winder et al. 1998).

FUNCTIONAL CONSEQUENCES OF SIGNAL AMPLIFICATION

The hallmark of highly amplified biochemical systems is that they tend to create a step function for triggering an effect, in this case LTP. An additional implication of the extensive serial, feedback, and cross-talk effects of one signal transduction mechanism on another in LTP is that it is essentially impossible to selectively inhibit any one enzyme involved in LTP induction. Even an absolutely selective inhibitor (or genetic manipulation) is likely to have pronounced secondary consequences on the other signal transduction molecules involved in LTP induction. This is one reason why multiple lines of experimental evidence, such as those presented as criteria 3 and 4, are so important as adjuncts to inhibitor studies.

Theme Two—Signal Integration

TEMPORAL INTEGRATION

It is important to keep in mind that all of the processes diagramed in Figure 1 are not terminated instantaneously, but typically decay with a half-life on the order of minutes. Thus, delivery of one tetanic stimulus may serve to amplify subsequent temporally spaced stimuli, allowing for temporal integration of signals (see DeKoninck and Schulman 1998). This is likely to be the means by which multiple, spaced tetanic stimuli are able to selectively produce late-phase LTP.

FUNCTIONAL INTEGRATION

An additional consideration is that many of the protein kinases outlined in Figure 1 converge on the same substrates. Probably the best example of this is CaMKII and PKC phosphorylation of AMPA receptors. Strikingly, CaMKII and PKC phosphorylate the identical amino acid on GluR1 AMPA receptors, a post-translational event that increases current through the receptor (Mammen et al. 1997). Thus, the AMPA receptor serves as a functional integrator of inputs from the PKC and CaMKII pathways. This is likely to explain the experimental observation that simultaneous inhibition of both PKC and CaMKII is necessary to reverse the expression of E-LTP (Wang and Feng 1992).

CONSEQUENCES OF SIGNAL INTEGRATION

The net effect of signal integration mechanisms such as those described above is to allow disparate stimuli to achieve additive, synergistic, or redundant effects in the induction or expression of LTP.

Theme Three—Signal Divergence

Protein kinases are pluripotent molecules. Activation of a single subtype of protein kinase typically elicits changes in a wide variety of downstream cellular targets. To pick just one example in the context of LTP, PKA can regulate AMPA receptors, voltage-dependent K^+ channels, voltage-dependent Ca^{2+} channels, and gene transcription (through CREB phosphorylation). Thus, through the pluripotency of protein kinases, a single molecular signal can produce broadly divergent responses in the

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cell. The functional consequence is that activation of a single signaling cascade can produce a multicomponent but coordinated molecular response that is geared toward a unified cellular outcome.

Before concluding, I would like to briefly discuss one additional topic. A reasonably large number of LTP experiments have been performed looking at biochemical changes resulting from LTP-inducing stimulation. Measuring correlative changes in this fashion is subject to the criticism that the observed changes may simply be epiphenomena (Sanes and Lichtman 1999). I assume that what is meant by this criticism is that the observed change may not be causally related to increasing synaptic strength, at least by any mechanism we can conceive of at the present time. My *bias* is that true biochemical epiphenomena, that is, stimulus-evoked events causally related to nothing, are rare. Nevertheless, the epiphenomenon criticism misses the point of these types of biochemical experiments on two counts. One is that, as described above, they test specific predictions of various models for how LTP works and indeed are a very powerful test in the context of additional data using inhibitors and activators of the pathway under study. A second goal of these types of experiments, which is often overlooked, is that they can give insights into the cellular locus of plastic changes.

As has been emphasized by one of the pioneers in this area, Aryeh Routtenberg, this second aspect is nicely illustrated by biochemical studies of the presynaptic protein GAP-43, also known as B50, F1, and neuromodulin, (Routtenberg 1990). There is very good biochemical evidence that PKC-mediated GAP-43 phosphorylation increases in LTP (Lovinger et al. 1985; Linden et al. 1988; Giannotti et al. 1992). Taking these GAP-43 data together with other biochemical evidence from studies of other presynaptic proteins (Malgaroli et al. 1995; Ryan et al. 1996), a strong case can be made that NMDA receptor-dependent, postsynaptically induced presynaptic changes occur in LTP. Are these changes causally related to increasing neurotransmitter release? In the case of GAP-43, probably not. But to dismiss the data on this basis is to miss the much more profound conclusion that can be drawn from the observation; neurons in the CNS are capable of retrograde signaling. This conclusion stands independent of whether or not increased neurotransmitter release contributes to the expression of LTP.

Concluding Comments

It is impossible to formulate a comprehensive molecular model of LTP at this time. This commentary serves as a first attempt at reducing the enormously complicated molecular picture of LTP to a manageable level by emphasizing a common vocabulary, outlining a set of criteria for categorizing molecular studies of LTP, and presenting an initial model for the core signal transduction mechanisms of LTP. My overriding goal has been to present an optimistic outlook on the state of our understanding of LTP through these devices.

As studies of synaptic function have proceeded from the peripheral to the central nervous system, one common characteristic of CNS synapses is their astounding plasticity. It is likely that many synapses in the CNS have no static, default level, but from the moment of formation are subject to regulation by plastic processes. In this light, an understanding of synaptic

function in the CNS cannot be derived independently of an understanding of the mechanisms of synaptic plasticity. In many respects studies of LTP are the driving force in advancing our understanding of basic synaptic biology in the CNS.

Should we have a moratorium on molecular studies of LTP (Sanes and Lichtman 1999), or should molecular studies proceed apace? I liken our assembling a complete molecular model for LTP to assembling a jigsaw puzzle. When putting together a puzzle you typically first find the edge pieces, which are readily recognizable by a single characteristic. When progressing to the interior of the puzzle one looks for patterns and colors to identify pieces to be able to group together and assemble known components of the overall picture. In the final stages one can many times identify the place for an individual puzzle piece simply on the basis of its shape being appropriate to fill an empty spot in the puzzle. At each stage different algorithms are used that lead to identification of the correct placement of pieces. At no stage in the process is one well-served by not having all the puzzle pieces available.

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This commentary is based on a lecture delivered at the 1999 Cold Spring Harbor Learning and Memory course. Before my lecture the students in the course had read the recent commentary by Sanes and Lichtman (1999), and one goal of my lecture was to present a rejoinder to this commentary. I wish to acknowledge Josh Sanes and Jeff Lichtman for their challenging commentary. I also wish to thank the faculty (Jack Byrne, Bai Lu, Robert Malinow, David Linden, Howard Eichenbaum, and Keir Pearson) and students of the Cold Spring Harbor Laboratory Learning and Memory course for many hours of thought-provoking questions, presentations, and discussions while I was there. Many of their thoughts and suggestions have been incorporated wholesale into this commentary. Finally, I invite readers to provide feedback on the commentary by e-mail. This work was supported by grants MH57014, HD24064, and NS37444 from the National Institutes of Health and a National Alliance for Research on Schizophrenia and Depression Independent Investigator Award.

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J. David Sweatt

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