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Long-Term Potentiation and Memory

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Lynch, MA. Long-Term Potentiation and Memory. *Physiol Rev* 84: 87–136, 2004; 10.1152/physrev.00014.2003.—One of the most significant challenges in neuroscience is to identify the cellular and molecular processes that underlie learning and memory formation. The past decade has seen remarkable progress in understanding changes that accompany certain forms of acquisition and recall, particularly those forms which require activation of afferent pathways in the hippocampus. This progress can be attributed to a number of factors including well-characterized animal models, well-defined probes for analysis of cell signaling events and changes in gene transcription, and technology which has allowed gene knockout and overexpression in cells and animals. Of the several animal models used in identifying the changes which accompany plasticity in synaptic connections, long-term potentiation (LTP) has received most attention, and although it is not yet clear whether the changes that underlie maintenance of LTP also underlie memory consolidation, significant advances have been made in understanding cell signaling events that contribute to this form of synaptic plasticity. In this review, emphasis is focused on analysis of changes that occur after learning, especially spatial learning, and LTP and the value of assessing these changes in parallel is discussed. The effect of different stressors on spatial learning/memory and LTP is emphasized, and the review concludes with a brief analysis of the contribution of studies, in which transgenic animals were used, to the literature on memory/learning and LTP.

I. INTRODUCTION

Learning may be described as the mechanism by which new information about the world is acquired, and memory as the mechanism by which that knowledge is retained. It is convenient to categorize memory as being explicit, which is defined as that involved in the conscious recall of information about people, places, and things, or implicit, which is characterized by the nonconscious recall of tasks such as motor skills. Explicit memory depends on the integrity of temporal lobe and diencephalic structures such as the hippocampus, subiculum, and entorhinal cortex. Implicit memory includes simple associative forms of memory, such as classical conditioning, and nonassociative forms, such as habituation, and relies on the integrity of the cerebellum and basal ganglia (582).

Although several areas of the brain play a part in consolidation of several forms of learning/memory (Table 1), the hippocampus has been recognized as playing a vital role in formation of declarative memory in particular, which describes the synthesis of episodic and semantic memories. The observations of Scoville and Milner in 1957 (556), showing that bilateral hippocampal removal as a treatment for epilepsy suffered by patient H.M., resulted in anterograde amnesia explicitly identified the importance of the role of the hippocampus and temporal lobe structures in memory. Since then, studies in humans (e.g., Ref. 585) and animals (e.g., Refs. 427, 473) have consolidated the essential finding of that study. More recently, noninvasive methods using direct brain imaging techniques such as magnetic resonance imaging and positron emission tomography (PET) characterized blood flow and oxygen use in the hippocampus and identified fluctuations in these parameters during learning tasks (e.g., Refs. 582, 584). This review focuses principally on a discussion of synaptic plasticity in the hippocampus and only briefly discusses synaptic plasticity in other areas.

TABLE 1. *Several brain areas play a role in learning and memory*

Type of Learning/Memory	Brain Areas Involved	Reference No.
Spatial learning	Hippocampus	33, 661
	Parahippocampus	662, 663
	Subiculum	427
	Cortex	
	Temporal cortex	
	Area 47	573
	Posterior parietal cortex	16
Emotional memory	Amygdala	522
Recognition memory	Hippocampus	484, 661
	Temporal lobe	34, 35
Working memory	Hippocampus	311
	Prefrontal cortex	
Motor skills	Striatum	582
	Cerebellum	
Sensory (visual, auditory, tactile)	Various cortical areas	427, 595
Classical conditioning	Cerebellum	484
Habituation	Basal ganglia	

A. The Hippocampus and Spatial Memory

One of the most compelling problems in neuroscience is to identify the mechanisms underlying memory, and although a great deal of progress has been made in the past few decades, it remains a significant challenge. Particular emphasis has been placed on analysis of changes that accompany and support spatial memory because of its dependence on hippocampus and because of the well-developed protocols that are available for its analysis. A variety of paradigms are available for investigation of spatial learning, and perhaps the most commonly used is the Morris water maze in which an animal's capacity to remember spatial cues is required to locate a hidden underwater platform (426). Using this paradigm in particular, numerous studies have identified an essential role for the hippocampus in spatial learning; in addition, several studies have built on the original observation of O'Keefe which identified the involvement of specific hippocampal pyramidal cells in encoding information about the location of an animal in a particular space (471). Rats with lesions of the hippocampal and parahippocampal areas perform particularly poorly in spatial learning tasks; in the case of the Morris water maze, although lesioned and nonlesioned rats perform in a comparable manner when the platform is visible, lesioned rats perform very poorly when the platform is not visible. It appears that the key role of the hippocampus in spatial learning is synthesis of the configuration of spatial cues, which is governed, at least to some extent, by temporal events (607). Significantly other forms of learning, like visual discrimination and taste aversion, are not affected by hippocampal lesions.

A careful analysis of performance in different spatial learning tasks has led to the suggestion that the integrity of connections between the hippocampus, subiculum, and cortical areas is necessary for synthesis of all components of spatial learning. Monkeys with large bilateral lesions of the medial temporal lobe, which approximated the damage sustained by H.M., exhibited severe memory impairment on the delayed nonmatching to sample task (420, 663). Impairment was less severe when damage was confined to the hippocampus compared with additional damage to the perirhinal, entorhinal, and parahippocampal cortical regions (33, 661–663, but see Ref. 444). Some (104, 439), but not all (10, 286, 439), authors have reported similar impairments in rats, but results are dependent on the precise nature of the task and the extent of the lesion (104).

Recognition memory can be investigated using the visual paired comparison task, which assesses preference

for exploring a new, compared with a familiar, object or picture. It has been reported that performance in this task is not impaired in amnesic patients with hippocampal damage, provided there was no delay between the first and second presentations of the stimuli; a deficit was observed when a delay was introduced (404). This emphasizes the temporal component of hippocampal-dependent memory referred to above. Similar impairments were observed in monkeys with lesions of the temporal lobe (35, 34) or hippocampus (484, 661). Data from the rat are less clearcut (439; but see Ref. 586), and therefore, the role of the hippocampus in recognition memory in mammals requires further elucidation.

Although much emphasis has been placed on assessing the role of hippocampus in memory formation, it is acknowledged that most areas of the cortex are probably capable of supporting various sorts of memory, for example, visual sensory memory, auditory sensory memory, and tactile memory; these are transient or temporary memories, and consolidation is required to enable formation of long-term memory. It has also been shown, using PET in human subjects, that spatial memory is associated with differential activation in area 47 of the prefrontal cortex (573) and that lesions of the posterior parietal associative cortex lead to profound impairments (16).

Working memory, i.e., the ability to maintain and use mental representation for goal-directed behavior, is dependent not only on hippocampus but also on the prefrontal cortex, which has strong connections to the hippocampus. The frontal cortex also plays a significant role in the temporal ordering of spatial and nonspatial events and the planning of responses, and the integrity of other areas of the brain has been identified as being critical for formation of specific memory forms. For instance, the acquisition of motor skills and habits and the memories associated with such skills (procedural memory) relies on the integrity of the striatum and the cerebellum, while the role of the amygdala in emotional memory has also been recognized for many years. The recognition that several areas other than hippocampus, particularly cortical areas, play such an important part in various forms of memory prompted anatomical studies, and therefore, hippocampus-neocortical connections have been studied with great interest. It has been shown that, in addition to the hippocampal-prefrontal cortical connections which are routed through the subiculum, CA1 projects directly to the medial and orbital prefrontal cortices (40). The subiculum also receives inputs from the postsubiculum and entorhinal cortex, and it appears to play a role in processing and integration of the information that it relays to other cortical areas. These connections mean that the subiculum receives positional, directional, sensory, and contextual information. It has been shown that lesions of this area lead to deficits in certain forms of learning (551). In addition to the projection to subiculum, CA1 neurons project to the perirhinal, postrhinal, and entorhinal cortices, and a number of studies have suggested that these pathways play a role in various forms of learning and memory (472). Current evidence suggests that positional information relies on hippocampal-subicular interaction, directional information on the interaction between postsubiculum and subiculum, and sensory information on the interaction between entorhinal cortex and subiculum (472; see below).

While recognizing the primary role of the hippocampus in memory formation, the interaction with cortical structures, particularly in the context of long-term storage of memories, remains an issue of debate, and it has been proposed that sequential activation of the hippocampus and neocortex may be involved in consolidation of memory. One proposal is that although the hippocampus may be largely responsible for recall of recent memories, the neocortex is primarily concerned with recall of more remote memories (582). This idea is linked with the view that the hippocampus allows for rapid learning, permitting the neocortex to undergo synaptic changes required for slow learning. One prediction emanating from the hypothesis that hippocampus and cortex are responsible for maintenance of short- and long-term storage of memory, respectively, is that recall of distant memories would be independent of the hippocampus and, consistent with this, it has been reported that remote childhood memories and general knowledge were not affected in individuals with hippocampal damage. However, data from a recent systematic study on individuals with lesions of the hippocampus, in some cases extending to the temporal cortex, revealed that the extent of the lesion (from that affecting only the CA1, CA3, and dentate gyrus to that involving the entire hippocampal complex and temporal lobe) dictated the degree of impairment in recall and, to some extent, the remoteness of the memory. The development of neuroimaging techniques has allowed further assessment of the role of the hippocampal complex in retrieval of distant memories, and the evidence suggests that activation of hippocampal circuits occurs even when very remote memories are elicited (446).

Analysis of this question in animals has revealed that sectioning the fornix, or damaging the hippocampus or entorhinal cortex, typically impaired very recent memory, but generally spared more remote memory. This suggests that the hippocampus is necessary for memory storage and retrieval for only a limited time after learning and that time-related modification of cortical connections allows for memory retrieval independent of the hippocampus (583). However, it has been pointed out that this might also be explained if representation of older memories was more diffusely distributed in hippocampus. In this case, temporally graded retrograde amnesia could be explained because a partial lesion of the hippocampus will spare a remote memory more than a recent memory, whereas

complete hippocampal lesions will affect recent and remote memories equally (445).

It is appropriate to state that while great emphasis has been placed on the role of the hippocampus in spatial memory, a number of studies have identified its importance in nonspatial memory tasks. For instance, in a recent paper, using social transmission of food preference, Clark et al. (104) reported the lesions of the hippocampus and subiculum resulted in anterograde amnesia and temporally graded retrograde amnesia.

B. Synaptic Modifications and Memory

Activity-dependent synaptic plasticity plays a vital role in sculpting synaptic connections during development and has been identified in several synaptic pathways. Although it occurs, in particular, during critical periods of early development, it is also a feature of the adult brain. For example, it is widely accepted that memory formation is dependent on changes in synaptic efficiency that permit strengthening of associations between neurons; indeed, activity-dependent synaptic plasticity at appropriate synapses during memory formation is believed to be both necessary and sufficient for storage of information. Cajal (80) originally hypothesized that information storage relies on changes in strength of synaptic connections between neurons that are active. Hebb (221) supported this hypothesis and proposed that if two neurons are active at the same time, the synaptic efficiency of the appropriate synapse will be strengthened. An enormous effort has been channelled into understanding the mechanism by which strengthening of synaptic connections can be achieved and, in this effort, the importance of one model, above all others, cannot be overestimated; this model is long-term potentiation (LTP).

In 1966, Lomo (340) reported that a single, short test shock, following an initial period of conditioning test shocks to the perforant path, elicited a potentiated response in the dentate gyrus. The first full description of LTP by Bliss and Lomo in 1973 (64) reported that trains of high-frequency stimulation to the rabbit perforant path caused a sustained increase in efficiency of synaptic transmission in the granule cells of the dentate gyrus. This report, and others which followed during the 1970s, confirmed the Hebbian nature of this form of synaptic plasticity, and it was immediately recognized that the synaptic changes that underpin certain forms of learning and memory may be similar to those upon which expression of LTP relied. The three well-described characteristics of LTP, cooperativity, associativity and input specificity (see Ref. 62), and the durability of LTP (8), have been identified as solid arguments that support the hypothesis that LTP may be a biological substrate for at least some forms of memory. Several other pieces of evidence have consolidated this view. *1*) LTP is most easily demonstrable in the hippocampus, an area of the brain known to be fundamentally important in memory acquisition. *2*) Rhythmic bursts of activity that induce LTP mimic naturally occurring theta rhythm recorded in the hippocampus during exploratory behavior (132, 208, 313, 527). *3*) Inhibitors of hippocampal LTP also block hippocampal learning and retention of tasks (425). *4*) Several biochemical changes that occur after induction of LTP also occur during memory acquisition (see below). However, a definitive demonstration indicating that memory consolidation requires induction of changes that resemble those necessary for induction of LTP remains elusive. Similarly, it remains to be clearly shown that induction of LTP will result in some form of memory consolidation.

At least two components of memory can be discerned: short-term memory, which endures for a few hours, and long-term memory, which persists for several days and often much longer. At the cellular level, the storage of long-term memory is associated with gene expression, de novo protein synthesis, and formation of new synaptic connections. Consistently, protein synthesis inhibitors can block persistent memory but leave short-term memory unaffected, suggesting that stable, long-lasting memories rely on gene activation that is triggered at, or close to, the time of the experience. Here, there is an interesting parallel between memory and LTP, since it has been revealed that LTP consists of distinct phases involving different molecular mechanisms. The early phase (E-LTP), which lasts 2–3 h, is independent of protein synthesis, while more persistent long-lasting LTP (L-LTP), which lasts several hours in vitro and weeks in vivo, requires synthesis of new proteins.

A series of fundamentally important findings made in the early 1980s profoundly affected the course of research in LTP and which, for the first time, provided some insight into the mechanisms by which LTP consolidation occurred. The first of these was the observation that LTP in CA1 was inhibited by the *N*-methyl-D-aspartate (NMDA) antagonist 2-amino 5-phosphonopentanoic acid (AP5) (107), and this, combined with the important discovery that NMDA receptor activation led to influx of calcium through a ligand- and voltage-sensitive calcium channel (27), triggered significant advances in understanding the cellular cascades initiated as a result of tetanic stimulation. It was later established that the majority of synapses which support LTP, in hippocampus and elsewhere, do so in an NMDA receptor-dependent fashion (see below), but that while the resultant increase in postsynaptic calcium concentration was both necessary and sufficient for expression of LTP, NMDA receptor activation, although required in many cases, was not sufficient to result in its induction (62).

Petersen et al. (493) addressed the question of whether LTP at individual synapses was induced in an

incremental manner or in an all-or-none manner. In this clever series of experiments, a pairing protocol was used which resulted in a small, nonsaturating amount of potentiation combined with the use of minimal stimulation techniques to activate single fibers. The data indicated that individual synapses had different thresholds, but that once threshold was achieved, the degree of potentiation did not vary, indicating that synapses responded in an all-or-none manner; potentiation was dependent on NMDA receptor activation. It was also shown that, although synapses exhibited a variation in the delay to potentiation, once initiated the response was rapid. These data led the authors to conclude that reaching threshold, in circumstances in which background noise is considerable, requires coincident priming of pre- and postsynaptic elements and suggested that this and the rapid onset of response might be explained by autophosphorylation of calcium/calmodulin kinase II (CaMKII) and the consequent insertion into the membrane of AMPA receptors (see below).

II. SEVERAL AFFERENT PATHWAYS SUPPORT LONG-TERM POTENTIATION

In addition to the principal afferent pathways in the hippocampus, several other afferent pathways have been shown to sustain LTP (see Table 2). One that has been of great significance in promoting the idea that synaptic changes which underlie LTP may also underlie memory is the projection from the thalamus to the amygdala.

A. The Amygdala

A great deal of evidence indicates that fear conditioning, which is a robust form of classical conditioning exhibited by rodents, is amygdala dependent; specifically, neuronal changes mediating the association between the conditioned and unconditioned stimuli occur in the lateral nucleus of the amygdala. Consistently, lesions of the amygdala have also been shown to result in deficits in fear conditioning (114, 200), while phthalic acid lesions of the nucleus basilis magnocellularis, from which there is a dense cholinergic projection to the basolateral amygdala, have been shown to lead to a profound deficit in inhibitory avoidance behavior (499). In humans, as well as animals, activation of the amygdala has been shown to be closely correlated with memory for both aversive and pleasant stimuli (213).

A number of recent findings have led to the suggestion that the amygdala is not a critical long-term information storage site but that its role is to regulate memory consolidation in other brain regions (401, 402). For instance, if the amygdala is lesioned after training, fear-motivated learning is partially retained while certain pharmacological agents when administered following training have been shown to modulate learning (641). It has been concluded that the amygdala is the locus of control for Pavlovian fear conditioning while its role in inhibitory avoidance is to modulate activity of other brain areas (641).

Compelling evidence supporting the hypothesis that LTP represents a valid model for learning/memory has proven to be an elusive goal, but recent analysis in the amygdala has been of major significance. The amygdala is the point of convergence of information from conditioned and unconditioned stimuli and, when the conditioned stimulus is an audible tone, the information is carried to the lateral amygdala via the afferent input from the auditory thalamus; this connection can express LTP (105). Pairing this conditioned stimulus with foot shock (the unconditioned stimulus) increases the response of amygdalar cells to auditory stimulation, and this was shown to be coincident with the animals exhibiting freezing behavior. This enhanced response of the cells was persistent and did not occur when the stimuli were unpaired (522). Predictably neuronal activity in the lateral amygdala was enhanced by the conditioned stimulus, and this preceded behavioral responses (514); more recently, it was shown that drugs that interfere with LTP in these pathways disrupt behavioral fear conditioning (61). Thus, with respect to at least one form of memory, a role for LTP has been identified, and it is important to point out that LTP in the amygdala shares several features with LTP in hippocampus. For instance, it has been shown that it is dependent on NMDA receptor activation, that retrieval of fear memories requires protein synthesis (447), and that activation of the transcription factor cAMP response element binding protein (CREB) is a key element in consolidation of memory, including fear memory (see sect. v*D*).

In an effort to explain the persistent nature of conditioning, it was proposed that the conditioned stimulus

TABLE 2. *Several pathways support LTP*

Auditory thalamus → amygdala (105)
Entorhinal cortex → dentate gyrus (64)
Mossy fibers → CA3 (348)
Commissural fibers → CA3 (see Ref. 62)
Schaffer collaterals → CA1 (107)
Hippocampus (CA1) → subiculum (110)
Hippocampus (CA1) → prefrontal cortex (141, 257)
Subiculum → prefrontal cortex (427)
Thalamus → layer IV cortex (227)
Mesocortical thalamic nucleus → medial prefrontal cortex (227)
Cortico-cortical pathways
Layer I → layer V (231)
Layer II → layer V (631)
Layer II/III → layer IV (215)
Cortex → striatum (medium spiny neurons; see Ref. 81)
Dorsolateral geniculate nucleus → visual cortex (229)
Parallel fiber → Purkinje neuron (see Ref. 343)

Reference numbers are given in parentheses.

evokes excitatory postsynaptic potentials (EPSP) at sensory input synapses onto pyramidal neurons of the lateral amygdala and that this coincides with depolarization of the same neurons by the unconditioned stimulus. As a consequence of the depolarization, calcium influx through NMDA receptor-associated channels occurs, amygdalar neurons fire action potentials which back-propagate into the dendrites, and this coincident activity, together with the EPSPs generated by the conditioned stimulus, leads to calcium entry through voltage-gated calcium channels. It has been proposed that the increase in intracellular calcium, consequent upon NMDA receptor-associated calcium channel opening, underlies short-term fear memory while the additional calcium entry through voltage-dependent calcium channels is required for long-term memory (61).

Both the hippocampus and entorhinal cortex receive direct projections from basolateral amygdala (497), and therefore, the recent reports indicating a modulatory role of the amygdala on hippocampal LTP have not been surprising. Activation of the basolateral amygdala has been shown to enhance LTP in dentate gyrus (13, 245), but lesions result in impaired LTP (244). Significantly, activation of the basolateral nucleus of the amygdala (within a specific time window) has the capability of transforming short-term potentiation in dentate gyrus of freely moving rats into protein synthesis-dependent persistent LTP. The authors found that this effect was independent of direct activation of glutamatergic inputs and proposed that the convergence of the action of a modulating transmitter as a consequence of amygdalar stimulation and glutamatergic activation following perforant path stimulation was necessary for consolidation of persistent LTP (167). In parallel with its modulatory effect on LTP, amygdalar activation has also been shown to enhance hippocampal-dependent learning (214, 481, 524); however, LTP (and short-term potentiation) in CA1 has been shown to be reduced in slices prepared from rats that were previously exposed to contextual fear conditioning (535).

Emerging evidence has indicated that an intact basolateral amygdala underpins stress-induced modulation of hippocampal LTP (290). Thus lesioning studies have revealed that the inhibitory effect of stress on LTP is suppressed in rats following electrolytic lesions of the amygdala (290), while the poorer performance in spatial learning, which is induced by adrenalectomy (523-525) or stress (290), is dependent on an intact amygdala. Similarly, electrolytic lesions of the amygdala abrogated the behavioral effect of stress induced by restraint and tail shock (290). There is evidence that this modulatory role of the amygdala involves activation of the projection of the stria terminalis to the nucleus accumbens (523).

While the auditory thalamus projects to the lateral amygdala, the mediodorsal thalamic nucleus projects to the medial prefrontal cortex (mPFC); the latter pathway has been shown to support both LTP and long-term depression (LTD), and evidence favors the idea that learned fear may be dependent on plastic changes at these synapses. Thus it appears that extinction of learned fear is associated with LTP in mPFC, while persistence of LTD during extinction is coupled with a return of the learned fear behavior (227).

B. The Visual Cortex and the Somatosensory Cortex

It has been proposed that the mechanisms which underlie LTP and LTD in visual cortex and somatosensory cortex play a contributory role in experience-dependent synaptic plasticity. In the case of the visual cortex, experience-dependent acquisition of visual responsiveness during the critical period requires significant modification of synaptic connections. Synaptic modification depends on neuronal activity, and like LTP in visual cortex and elsewhere (24), threshold stimulation in somatosensory cortex is required to permit synaptic changes. A pivotal role for NMDA receptor activation in LTP induction has been described in both areas, and the profound modifications in synaptic plasticity that occur in early life have been attributed to NMDA receptor subunit expression which alters with maturity (50, 51, 162, 619). Significantly, it has been shown that NMDA-sensitive LTP can be elicited in the adult rat visual cortex in vivo by stimulation of the dorsal lateral geniculate nucleus and that the cortical response to visual stimuli is enhanced after LTP (229). The physiological consequences of the enduring nature of this form of plasticity remain to be established, but if it is the case that experience-dependent plasticity and LTP share common mechanisms, then deficits which occur as a result of visual deprivation during the critical period may be reversible in adulthood.

Development of the barrel cortex is a striking example of synaptic plasticity that is dependent on experience-dependent changes in thalamocortical circuits. Layer IV of the rat somatosensory cortex has a topographic map representing peripheral receptor density, formation of which is exquisitely sensitive to receptor stimulation particularly during development. The thalamocortical synapses of layer IV cortical cells support LTP (156), although it is not clear whether LTP is involved in the plasticity required for formation of topographic maps. However, like use-dependent synaptic modification and LTP in visual cortex, LTP in the developing barrel cortex requires NMDA receptor activation (156), whereas inhibition of the NMDA receptor by AP5 blocks the functional changes associated with mystacial whisker ablation in the neonate (552). The role of the NMDA receptor has been further underlined by the observation that formation of cortical barrels is prevented in the absence of the NR1

subunit in cortical neurons (253), although expression of the NR2 subunit appears to be without effect on plasticity in either visual cortex (495) or barrel cortex (344).

C. The Prefrontal Cortex

Training in an associative learning task was found to be accompanied by enhanced synaptic transmission in hippocampal-prefrontal cortical synapses (141); while early changes in synaptic transmission in hippocampal synapses were recorded, changes in prefrontal cortex were delayed. This is consistent with the idea that the hippocampus plays a special role in rapid learning and acts in concert with the cortex to ensure stabilization of a cortical representation of learned events. Restricted lesions of the prelimbic area of the prefrontal cortex suggest that this area is critically involved in working memory (see Ref. 311).

Consolidation of the hypothesis that the cellular mechanisms underlying LTP are necessary for memory formation would be assisted if it could be shown that pathways that are activated during memory formation sustain LTP. The importance of hippocampal-prefrontal cortex communication in cognition has been recognized for many years (312, 314, 582), and one of the first descriptions of LTP outside the hippocampus was made in the hippocampal input to the prelimbic cortex in vivo (141). LTP in this pathway has been reported several times since the initial report (e.g., Ref. 257), and it has been demonstrated that it requires NMDA receptor activation (257). Like LTP in hippocampus, there is emerging evidence that activation of protein kinase A (PKA) at these synapses leads to CREB activation (see Ref. 311).

In addition to the hippocampal-prefrontal cortical pathway, other cortical pathways have also been shown to support LTP. For instance, LTP can be induced in layer V following stimulation of layer I (231) or layer II (631) and in layer IV following stimulation in layer II/III (215). Although NMDA activation is necessary for expression of LTP in hippocampal-cortical synapses, characterization of the mechanisms underlying LTP in cortico-cortical pathways remain to be clarified. For instance, some authors have reported that NMDA receptor activation is required, whereas others have disputed this (215, 226).

D. The Subiculum

In addition to the direct projections (40), some hippocampal-prefrontal cortical connections are routed through the subiculum (20), an area of the brain which plays a role in processing and integration of information that it relays to other cortical areas. Thus the circuits that connect the subiculum to the presubiculum, the perirhinal cortex, the entorhinal cortex, and the prefrontal cortex have been identified as significant in particular forms of memory and learning, for example, instrumental learning (36), working memory (177), avoidance learning (178), and visual, tactile, and spatial memory (427, 595, 662). Significantly, several of these subicular pathways have been shown to support LTP (110, 296). Perhaps the best characterized is the CA1 to subiculum projection which exhibits paired pulse facilitation and LTP in vivo (110, 472) and in vitro (296). Analysis of subicular unit firing in a pellet-chasing task revealed the existence of place cells in the subiculum, although the firing fields were less discrete than those described in CA1 (471, 560). The expression of synaptic plasticity and the evidence of a representation of space in the subiculum, together with the observations that lesions of the area lead to deficits in spatial learning (427), indicate that, like the hippocampus, the subiculum appears to play a significant role in learning and memory.

III. MECHANISMS UNDERLYING LONG-TERM POTENTIATION

A. NMDA Receptor Activation and LTP

The critical event leading to induction of LTP appears to be the influx of calcium ions into the postsynaptic spine and therefore, predictably, LTP is blocked by injection of EGTA (352b) or BAPTA (433) and induction occurs when the postsynaptic cell is loaded with calcium (370). Therefore, it is agreed that elevation of postsynaptic calcium concentration is both necessary and sufficient for the induction of hippocampal LTP (62).

In the majority of synapses that support LTP (in the hippocampus and elsewhere), the postsynaptic increase in calcium is mediated through activation of the NMDA receptor. Several experimental approaches have been used to consolidate the initial evidence which supported this contention, and some of these are listed in Table 3. Significantly, the characteristics of NMDA receptor activation eloquently explain the properties of LTP: receptor activation leads to opening of the associated calcium channel when occupied by glutamate and when the postsynaptic membrane is depolarized. Therefore, the NMDA receptor complex is dually regulated by ligand and voltage and thereby acts as a coincidence detector. Consistent with its pivotal role in LTP induction are numerous demonstrations that inhibition of NMDA receptor activation blocks LTP. The first of these demonstrations in CA1 in vitro and dentate gyrus in vivo, using the specific competitive NMDA receptor antagonist AP5 and the noncompetitive NMDA-associated channel blocker MK801 (106, 107, 153), was followed by several confirmatory reports. With the exception of mossy fiber-CA3 synapses, induction of LTP in all subfields of the hippocampus is

TABLE 3. *Activation of NMDA-R and mGluR play a role in LTP and learning/memory: some key findings*

Receptor	Role in LTP and Learning/Memory
NDMA	NMDA antagonists inhibit LTP and spatial learning (107, 427)
	NR2A disruption leads to attenuated LTP and impaired spatial learning (293, 539)
	NR2B disruption leads to attenuated LTP (302)
	NR2B overexpression enhances LTP and spatial learning (604)
mGluR	ACPD enhances LTP (403)
	ACPD induces potentiation of synaptic response (100)
	mGluR type I antagonists block LTP and impair spatial learning (23, 374)
	mGluR-associated signaling increases following induction of LTP (263, 346)
	mGluR knockout mice exhibit impaired LTP (not in mossy fiber → CA3) (348)

Reference numbers are given in parentheses.

NMDA dependent, although it has been shown that LTP in CA1 can be induced without the participation of NMDA receptors; in this case, the increase in postsynaptic calcium concentration is a consequence of activation of voltage-operated calcium channels, and therefore, calcium channel inhibitors suppress this form of LTP (209).

NMDA activation alone does not induce LTP (280). This observation, together with the demonstration that thapsigargin, which depletes intracellular calcium stores, inhibits LTP (72), suggests that calcium release from intracellular stores augments NMDA receptor-mediated calcium influx. Activation of the NMDA receptor may be critical for induction of many forms of LTP, but it is not necessary for all. In contrast, current evidence is consistent with the hypothesis that a rise in intracellular calcium concentration is a necessary element for the induction of all forms of LTP described to date.

In parallel with the importance of NMDA receptor activation in induction of LTP in hippocampus, it has been repeatedly shown that AP5 markedly attenuates performance in spatial learning tasks (e.g., Ref. 425), although it is now clear that previous exposure to similar tasks alters sensitivity to these inhibitors (see sect. III*B*). Activation of NMDA receptors seems to be necessary not only for acquisition of spatial information, but also for memory retention (240).

The requirement for NMDA receptor activation is not confined to plasticity in the hippocampus, since receptor blockade leads to a deficit in long- and short-term memory of fear conditioning (521, 634). Similarly, NMDA receptor activation is necessary for induction of LTP in amygdala, although LTP in amygdalar interneurons is NMDA independent (376). In addition to the amygdala, experience-dependent synaptic modifications and LTP in visual cortex (50, 51, 162, 229, 619) and frontal cortex (257) rely on activation of NMDA receptors.

Analysis of the subunit composition of the NMDA receptor has revealed differential expression of NR1 and NR2 with brain area, development, and activity (557, 637), and gene targeting has allowed examination of some of the physiological roles of the different subunits. Both hippocampal LTP and spatial learning rely on expression of NR2A, since disruption of this subunit is associated with deficits in both (293, 539), while deletion of the gene encoding NR2B also resulted in impairment of LTP in hippocampus as well as impairment in development of the barrel organ in the trigeminal complex (302, 321). Similarly, mutant mice lacking NR2A exhibit normal responses in tone-dependent fear response (i.e., a hippocampal-independent learned response) but exhibited deficits in contextual fear learning (a hippocampal-dependent response; Ref. 293); this finding discriminates between two forms of fear learning on the basis of their dependence on hippocampal function. In addition to the effects of disruption of NR2 subunits, genetic disruption of the NR1 subunit also leads to impairments in LTP and spatial learning (617, 618). Conversely, overexpression of the NR2B subunit was found to be associated with enhanced LTP and enhanced learning and memory (604). Analysis of the dynamics of different NMDA receptor subunits has revealed that visual experience results in insertion of new receptors with a higher proportion of NR2A subunits, resulting in an increase in the ratio between NR2A and NR2B (505). One consequence of this is that NMDA receptor-associated currents are shortened and, therefore, conditions will favor induction of LTD rather than LTP; this is consistent with the idea that an LTD-LTP modification threshold monitors plasticity and that this threshold alters with maturity (49).

B. NMDA Receptor Activation, Learning, and Memory

A great deal of evidence indicates that NMDA receptor activation plays an essential role in the acquisition of spatial memories. The first data that addressed this question were reported in 1986, when Morris et al. (425) found that blocking the NMDA receptor with AP5 inhibited spatial learning. The specific importance of the finding at that time lay in the fact that this agent also inhibited LTP, and therefore, this suggested an overlap in the mechanisms by which LTP was sustained and by which spatial learning was consolidated. Others, using genetically manipulated mice, arrived at essentially the same conclusion; for example, Tsien et al. (618) generated a mouse in which NMDA receptor was knocked out in CA1 and they reported that these mice exhibited impaired spatial memory, while nonspatial memory was intact, and this was coupled with a deficit in LTP. Similarly, both spatial learning and LTP were impaired in mutant mice that lacked the

NR2A (ε1) subunit (539). Conversely, overexpression of the NR2B subunit yielded mice with enhanced LTP and enhanced learning and memory (604, 605). These genetic correlations between LTP and some forms of learning and memory therefore support the initial findings of Morris et al. (425). However, more recent studies have revealed that inhibition of the NMDA receptor only impairs spatial learning in task-naive animals, whereas pretraining in a spatial task overcomes the inhibition induced by AP5 (39) or another potent and specific NMDA antagonist, NPC17742 (545), even when LTP in dentate gyrus was inhibited. Interestingly, Bannerman et al. (39) reported that pretraining in a nonspatial task induced a similar effect. It was subsequently shown that pretraining in a spatial learning task prevents disruption of a subsequent training session in spatial learning after saturation of LTP (478). It was concluded that all the components of spatial learning (at least in the Morris water maze) do not require NMDA receptor activation. In terms of the question of uncoupling of spatial learning and LTP, it was proposed that spatial learning can take place in the absence of LTP provided episodic aspects of the training context are familiar.

C. Metabotropic Glutamate Receptors and LTP

The first indication of a possible role for metabotropic glutamate receptors in LTP was in 1991 with the observation that the nonselective mGluR agonist 1-amino-1,3-cyclopentanedicarboxylic acid (ACPD) enhanced LTP (403); these findings were subsequently replicated by other groups (375, 512, 513). ACPD was later shown to induce a long-lasting potentiation of the synaptic response in CA1 (71, 72, 100, 374) and in the dentate gyrus (464), and the effect was shown to rely on calcium-dependent changes and on activation of protein kinase C (PKC), since it was prevented by thapsigargin and staurosporine (73). Although it has been reported that mGluR inhibition blocks LTP, this is not a consistent finding (see Ref. 23), and mutant mice have been generated in an effort to identify the precise nature of the dependency of LTP on mGluR activation. One study reported that LTP in CA1 of these mice was unimpaired (111), but another reported that it was blocked (11). Mutant mice lacking mGluR5 have been reported to show attenuated LTP induction in CA1 and dentate gyrus, but LTP in mossy fiber-CA3 synapses was spared, leading the authors to suggest that the modulatory effect of mGluR activation on LTP differed in NMDA-dependent and NMDA-independent pathways (348). It was subsequently shown that potentiation of the NMDA response was absent in mGluR5 mutant mice but that potentiation of the AMPA response was preserved (262); these findings led the authors to conclude that activation of mGluR5 plays a pivotal role in expression of NMDA receptor-dependent LTP. The impaired potentiation of the NMDA receptor-associated response in mGluR5 mutant mice has been identified as being PKC linked, since it could be overcome by activation of PKC (see Ref. 263). One proposed mechanism by which this effect occurs involves PKC-induced activation of *src*, which increases NMDA receptor-associated channel opening (346), although an alternative substrate for PKC may be *homer*, which couples mGluR5 to PSD 95 by formation of a cluster with another postsynaptic density protein, Shank (620). LTP has also been assessed in mutant mice lacking mGluR1, and there is certain confusion with respect to mossy fiber-CA3 LTP; one group reported that LTP was absent in mutant mice lacking mGluR1 (111), but this was not supported by the findings of a second group (234). Thus, although mGluR activation appears to contribute to expression of LTP (see Table 3), clarification of the roles of the different receptor groups is necessary (for example, see Refs. 111, 234, and 382).

Several groups have shown that spatial learning is dependent on mGluR activation (46, 70, 111, 348, 517), and inhibitory avoidance and contextual fear learning have also been shown to be dependent on receptor activation (11, 60, 103, 456). Specifically, the mGluR1 antagonist α-methyl-4-carboxyphenylglycine (MCPG) reduced spatial learning, whereas a class I agonist *trans*-azetidine-2,4-dicarboxylic acid (tADA) applied after learning facilitated memory recall (171, 510, 611). Consistently, 4-carboxyphenylglycine (4-CPG), a more selective class 1 antagonist, which blocked LTP, also inhibited learning and memory in some tasks (37). Consistent with these findings is the observation that mGluR5 mutant mice exhibited an impairment in spatial learning, as assessed by performance in the Morris water maze, and also in contextual fear conditioning; both forms of learning are dependent on an intact hippocampus (263). Interestingly, it was also reported that there was a persistent increase in mGluR5 expression after fear conditioning (511). This role for mGluR5 in fear conditioning is consistent with the earlier finding that 1-aminoindan-1,5-dicarboxylic acid (AIDA) resulted in a retention deficit in conditioning to the context but not the cue (103). In contrast to the change in mGluR5 expression, Reidel et al. (511) reported that there was no change in mGluR1 expression after fear conditioning, although an increase in mGluR1 mRNA has been observed after induction of LTP in dentate gyrus (611).

IV. WHAT SIGNALING EVENTS FOLLOW *N*-METHYL-D-ASPARTATE RECEPTOR ACTIVATION?

A. A Role for CaMKII in LTP

When it was established that increased calcium concentration in the postsynaptic cell, as a consequence of

NMDA receptor activation, was a critical factor in the induction of LTP, attention turned to analysis of the downstream cellular consequences of this increase. Among the early findings was that postsynaptic entry of calcium led to activation of CaMKII; this observation turned out to be a finding of major importance. CaMKII is one of the most abundant proteins in neurons comprising 1–2% of the total. Although it is expressed presynaptically and postsynaptically, its expression is particularly high in the postsynaptic density, where it is ideally located to respond to changes in calcium concentration. There are more than 30 isoforms of CaMKII and numerous substrates, many of which are located in the postsynaptic density (see Ref. 159). CaMKII appears likely to be a mediator of primary importance in linking transient calcium signals to neuronal plasticity.

In 1989, two groups reported the important finding that inhibitors of CaMKII blocked LTP in CA1 (369, 373). Since that time, the requirement for CaMKII activation in expression of LTP has been confirmed many times using many different approaches. Thus it has been shown that CaMKII activation is triggered by the LTP-induced NMDA receptor-driven increase in intracellular calcium and that activation of the kinase persists after induction of LTP (176, 479). This persistent activation of CaMKII occurs as a result of autophosphorylation at Thr-286, and it has recently been shown that if the kinase is mutated at this residue (by replacement of threonine with alanine), then autophosphorylation is prevented; in these circumstances, both LTP and spatial learning are impaired (194). These findings and a range of related findings, specifically those obtained from analysis of changes in transgenic mice, provide convincing evidence that CaMKII activation is necessary for expression of LTP. Significant among these reports are the observations by Silva and colleagues (570, 572), who demonstrated that deletion of the CaMKII gene in mice resulted in impairment in LTP and also impairment in spatial memory. Similarly, introduction of an activated calcium-independent form of CaMKII into CA1 neurons potentiated synaptic transmission and occluded LTP (219, 337, 494). However, LTP in CA1 in transgenic mice expressing a constitutively active calcium-independent mutant form of CaMKII (α-CaMKII^{T286A} mice) was similar to that in wild-type mice (388, 389), a surprising result if it is argued that CaMKII alone is sufficient to induce LTP. It was established that, in these mice, the threshold to induce LTP was increased, while the threshold to induce LTD was reduced, suggesting that the extent of activation of CaMKII was important in modulating the response to stimulation. These findings were elaborated upon and clarified in a recent study. Using transgenic mice in which the level of transgene expression was regulated, Bejar et al. (53) reported that expression of the transgene was associated with significant impairments in contextual fear conditioning and in spatial memory. The authors also reported that the level of expression of the transgene was important; significantly, LTP, induced by 5-Hz stimulation, was enhanced in mice expressing low levels of the transgene but was markedly depressed in mice expressing high levels of the transgene (53). The idea that the degree of stimulation of CaMKII may have a modulatory effect on plasticity has also been addressed in another study. In this case it was proposed that CaMKII may act as a memory molecule. Thus a strong stimulus can prime CaMKII so that subsequent stimuli can lead to greater association with the postsynaptic density (562).

The requirement for CaMKII activation in expression of LTP is therefore generally accepted, and there is strong evidence suggesting that activation of CaMKII is sufficient to induce LTP. Evidence favoring the view includes the demonstration that injection of a constituitively active form of CaMKII induces LTP (337, 494). A similar conclusion was drawn in experiments that used occlusion to address the question; thus cells that exhibited synaptic potentiation induced by CaMKII were insensitive to tetanic stimulation, and vice versa (335). Perhaps the most powerful arguments used to support the view that CaMKII is sufficient to induce LTP have been developed on the back of the "silent synapse" theory of LTP (see below). The increase in responsiveness to applied glutamate following LTP, which is due largely to increased AMPA conductance, is a consequence of CaMKII-induced phosphorylation of GluR1 on Ser-831 (125), and it has been proposed that this contributes to the LTP-associated increase in conductance (120). Of importance is the observation that the increase in GluR1 phosphorylation that accompanies LTP is inhibited by CaMKII antagonists. In addition, there is now compelling evidence to suggest that delivery of AMPA receptors to the spine after induction of LTP, allowing the transition from silent to nonsilent receptor, is closely linked with, and may even be dependent on CaMKII activation (324, 564, 565; see below and see Fig. 1).

In addition to the pivotal role for CaMKII in LTP, evidence has been emerging which suggests that CaMKIV may also play a role. CaMKIV, which is localized predominantly in neuronal nuclei, modulates CREB-regulated gene expression during LTP in CA1. Its activity is transiently increased after induction of LTP and is accompanied by increased phosphorylation of the transcription factor, CREB, and increased expression of the immediate early gene c-*fos* (275). Transgenic mice, in which the expression of a dominant-negative form of CaMKIV was restricted to the postnatal forebrain, exhibited a deficit in L-LTP but not E-LTP. In parallel with the impairment in LTP, CREB phosphorylation and c-*fos* expression were significantly attenuated in these mice (274).

Identification of the cellular events leading to activation of CaMKII after NMDA receptor activation has been

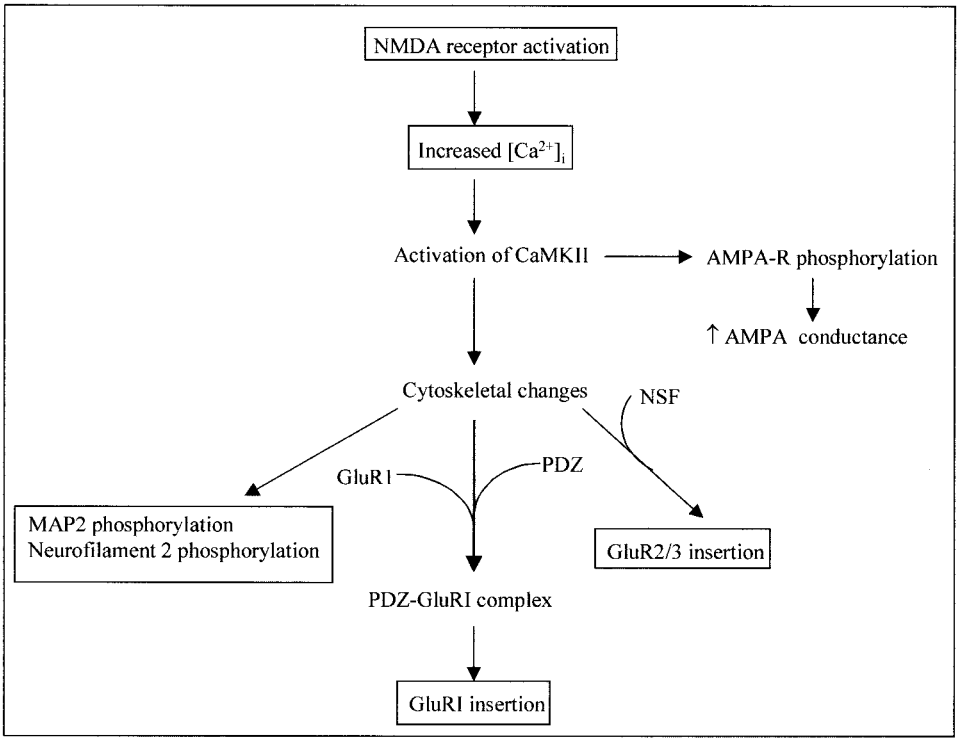

FIG. 1. Among the consequence of the increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) which accompanies *N*-methyl-D-aspartate receptor (NMDA-R) activation is increased calmodulin kinase II (CaMKII) activity which exerts multiple actions. One significant effect is increased AMPA conductance as a result of AMPA receptor (AMPA-R) phosphorylation and increased recycling of AMPA-R, which is due to CaMKII-induced changes in cytoskeletal proteins (see text for details). NSF, *N*-ethylmaleimide-sensitive factor.

a subject of intense interest. CaMKII binds to several postsynaptic density proteins including α-actinin and PSD95 and the synaptic adhesion molecule, densin-180. CaMKII activation has also been shown to lead to phosphorylation of microtubule-associated protein 2 (MAP2) and neurofilament L, both of which play a role in cytoskeletal regulation; on the basis of these findings, it has been proposed that CaMKII activation may contribute to the morphological changes that accompany the more persistent components of LTP (see below). However, it is important to recognize that there are several CaMKII substrates on the presynaptic side of the synapse; these include synapsin, synaptotagmin, and synaptophysin, which play a role in neurotransmitter release. The significance of this is that LTP, at least in dentate gyrus, has been coupled with enhanced transmitter release (see Refs. 62, 353). On the postsynaptic side of the synapse, current evidence suggests that NMDA receptor activation leads to translocation of CaMKII from dendrites, where it is associated with actin, to the postsynaptic density; it has been proposed that this requires calcium but not autophosphorylation (159). It seems that binding to the NR2B subunit occurs and that this leads to increased association of calmodulin with CaMKII and, subsequently, an increased association with the postsynaptic density (48).

B. A Role for CaMKII in Learning/Memory

In parallel with the finding that CaMKII activation is necessary for induction of LTP, several studies have indicated that activation of CaMKII is required for consolidation of various forms of memory. For instance, heterozygote mice in which CaMKII expression was reduced by ~50% exhibited normal hippocampal-dependent memory initially after training, but it was reported that memory 10–50 days after training was significantly impaired (164). Similarly, spatial learning has been shown to be impaired in α-CaMKII^{T286A} mice (194). Interestingly, hippocampal place cells are unstable in α-CaMKII^{T286A} mice, and it has been proposed that this may significantly impact on spatial learning (101, 335). The situation with respect to a role for CaMKIV in memory requires clarification. One report has indicated that the deficit in LTP in CaMKIV transgenic mice was correlated with an impairment in long-term memory (i.e., consolidation/retention rather than acquisition; Ref. 274), but it has also been reported that targeted gene disruption of CaMKIV, which resulted in impaired LTP in CA1 coupled with impaired CREB phosphorylation, was not associated with any evidence of deficits in spatial learning or memory (232).

The dependence of plasticity in the somatosensory cortex on CaMKII activation has been assessed by deletion of CaMKII and by assessing changes in α-CaMKII^{T286A} mice. Both sets of animals failed to exhibit plasticity, and both were incapable of sustaining LTP (164, 196). These coupled findings suggest that this form of plasticity may be reliant on molecular changes that contribute to maintenance of LTP. A similar argument has been advanced with respect to plasticity in the visual cortex. In this case also, experience-dependent synaptic plasticity is mark-

edly attenuated in α-CaMKII^{T286A} mice (597). Consistent with the idea that CaMKII activation plays a role in fear conditioning, as it does in spatial learning, are the observations that transgenic animals with regulated expression or deficits of CaMKII demonstrate impairments in fear conditioning (571, 638), while fear conditioning is blocked by the CaMKII inhibitor KN62 (648). CaMKII activation also appears to play a role in other forms of learning. Thus intrahippocampal infusion of the CaMKII inhibitor KN62 caused full retrograde amnesia of inhibitory avoidance learning in rats, when given immediately, but not three or more hours after training (600), while activity of CaMKII was increased after training rats in a one-trial inhibitory avoidance task (see Ref. 254). Interestingly, an increase in the phosphorylation state of CREB in the hippocampus has been described after inhibitory avoidance training (57), and this finding, together with the observation that inhibition of CaMKII by KN62 prevents induction of the immediate early genes *zif268* and c-*fos* (577), provides an insight into mechanisms underlying the enduring nature of CaMKII-dependent learning.

The data obtained from the study of synaptic plasticity in CaMKII knockout mice has, to a large extent, been paralleled by data in other organisms; the clear message is that several models expressing various forms of synaptic plasticity exhibit a requirement for CaMKII activation. For instance, CaMKII knockout in *Drosophila* exhibits impaired associative learning, but motor and sensory systems remain unaffected (265). Similarly, knockout of unc43 (the CaMKII analog in *Caenorhabditis elegans*) affects the stability of synapses and general neuronal behavior, ultimately affecting function of olfactory neurons (536).

C. AMPA Receptors and LTP

The importance of AMPA receptors in fast excitatory synaptic transmission has been acknowledged for decades, and because of this, it has been recognized that modulation of AMPA receptor activity could significantly contribute to expression of LTP. The production of mutant mice expressing different receptor subunits provided some insight into the role of AMPA receptors, particularly in relation to control of calcium fluxes. Calcium entry is modulated by the GluR2 subunit of the AMPA receptor; specifically, high expression of GluR2 mRNA has been correlated with low calcium entry (186). Predictably, AMPA receptors assembled from GluR2 subunits, in contrast to those assembled from GluR1, GluR3, or GluR4 subunits, are impermeable to calcium ions (186). Thus AMPA receptor-associated calcium permeability is low in pyramidal and granule cells of the hippocampus where there is a relatively high expression of GluR2-containing AMPA receptors. LTP was found to be enhanced in GluR2 mutant mice (261), whereas LTP was markedly attenuated in mice lacking the GluR1 subunit (423); specifically, LTP in dentate gyrus was recorded, albeit attenuated, in GluR1 knockout mice, but it could not be induced in area CA1 (659).

A great deal of evidence has suggested that increased expression of AMPA receptors on the postsynaptic membrane is likely to be the primary requirement leading to expression of LTP. The initial finding suggesting that postsynaptic glutamate receptor expression might be modulated after induction of LTP came from analysis of LTP-associated changes in sensitivity of CA1 neurons to ionophoretically applied glutamate receptor ligands. The data indicated a slow increase with time after LTP induction (120), suggesting that LTP increased the sensitivity, or the number, of receptors. Subsequent evidence revealed that increased receptor number was responsible for this finding. The primary work leading to the development of the so-called silent synapse theory of LTP was initiated with the recognition that certain synapses were functionally silent because of a lack of AMPA receptors, although NMDA receptors were present (252, 323). Thus when single connections between CA3 axons and CA1 pyramidal cells were assessed, only NMDA receptor-generated excitatory postsynaptic currents (EPSCs) could be elicited in a proportion of CA1 pyramidal cells; however, stimulus paradigms that induced LTP resulted in the recruitment of AMPA receptor-generated responses (252, 323). This was interpreted as evidence that AMPA receptors were inserted into the postsynaptic membrane after induction of LTP. Since then, a great deal of evidence has been accumulated indicating that AMPA receptor expression on cells is a dynamic process and is controlled by a cycle of exocytosis and endocytosis (351, 372). It has also been repeatedly shown in cultured cells that this cycle is modulated by NMDA receptor activation which leads to increased recruitment of AMPA receptors and increased AMPA-mediated miniature EPSPs (324, 345, 565). Lu et al. (345) reported that the punctate expression of GluR1 which colocalized with synaptophysin was consistent with synaptic localization of the AMPA receptors. They further reported that activity-dependent expression of these receptors was blocked by NMDA receptor inhibition, by sequestering calcium in the cells using BAPTA or by application of tetanus toxin which inhibits exocytosis by cleaving vesicle-associated membrane protein (VAMP), the SNARE protein which is necessary for exocytosis.

It appears that there is a fairly constant turnover of AMPA receptors containing GluR2/3 subunits at the synapse and that delivery is dependent on their interaction with a number of cytoskeletal proteins including *N*-ethylmaleimide-sensitive factor (NSF; Refs. 458, 579). In contrast, GluR1-containing AMPA receptors are inserted into dendritic spines in an activity-dependent manner, and this

is associated with CaMKII activation and requires an interaction with a different family of postsynaptic density proteins (type II PDZ domain proteins; Refs. 496, 564). Indeed, it has been reported that activation of CaMKII drives synaptic incorporation of GluR1 subunits (see Ref. 578); however, it appears that the substrate protein is the PDZ domain protein that complexes with GluR1 to allow membrane insertion (220; see Fig. 1). In a recent study, it was shown that brain-derived neurotrophic factor (BDNF) may induce the accumulation of AMPA receptors at synapses previously devoid of these receptors, as has been proposed for silent synapses (406). Interestingly, while LTP has been linked to an increase in redistribution of AMPA receptor leading to increased membrane expression, there is also some evidence that NMDA receptor-dependent LTD is associated with a decrease in the proportion of surface-expressed synaptically localized GluR1 subunits (88).

Several groups have reported that induction of LTP is dependent on development; neonatal rats, up to postnatal day 8, are incapable of sustaining LTP, but this inability disappears shortly afterwards (47, 78, 147). In an interesting parallel it has been established that silent synapses demonstrate a developmental profile; thus the number of synapses expressing NMDA, but not AMPA, receptors in the hippocampus decreases with age (325).

Evidence for conversion of silent to functional synapses in plasticity associated with development has been accumulating, and the presence of silent synapses in developing cerebellar granule cells, which disappear as development progresses, has been documented recently (343). Similarly, during the so-called critical period, many thalamocortical synapses exhibit NMDA-, but no detectable AMPA-generated, receptor currents, suggesting the presence of functionally silent receptors. It has been proposed that LTP may lead to conversion of thalamocortical synapses from silent to functional and that this is fundamental in modulation of experience-dependent changes in thalamocortical circuits (156, 251). Silent synapses have also been identified in immature pyramidal neurons in the neonatal rat visual cortex, and these decrease during early postnatal development; the evidence suggests that, in this area also, the conversion from silent to functional synapses is dependent on NMDA receptor activation and occurs as a consequence of LTP-like activity (533).

D. Silent Synapses, Learning, and Memory

The initial findings that indicated an increase in AMPA receptors sensitivity after LTP induction sparked some parallel investigations in tissue prepared from animals that underwent training of various sorts. Thus Tocco et al. (613) reported that AMPA receptor binding was increased after training in a classical conditioning paradigm, but that no parallel change was observed in NMDA receptor binding. While facilitation of AMPA-mediated responses was shown to improve memory (204, 588), inhibition resulted in retrograde amnesia of inhibitory avoidance training in rats (82, 84, 260). A rapid and selective increase in the density of AMPA receptors in the hippocampus was also reported after training (82, 84), and recent evidence has indicated that this increase in binding reflected enhanced GluR1 expression (83). It was also shown that training led to a time-dependent increase in expression and activity of CaMKII and that this was accompanied by increased AMPA binding in hippocampal synaptosomal membranes and by increased GluR1 subunit phosphorylation (83).

V. INDUCTION OF LONG-TERM POTENTIATION ACTIVATES SEVERAL CELL SIGNALING CASCADES

Since the 1980s, many groups have concentrated their efforts with a view to identifying the signaling pathways that enable LTP to be sustained, and for several years a great debate continued about whether changes occurred presynaptically, postsynaptically, or both. It appears to this author that the predicted outcome, i.e., that changes occur on both sides of the synapse, has long been realized, and the following sections and Table 4 attempt to highlight at least some of the changes reported.

A. cAMP

Several studies have indicated that LTP is dependent on a cascade of cellular signaling events that are stimulated by an increase in intracellular cAMP concentration; these events include activation of PKA, which leads ultimately to activation of transcription factors such as CREB and translation. It has been shown that cAMP concentration and PKA activation are enhanced after induction of LTP and that LTP is inhibited by activators of PKA.

Earlier experiments tended to focus on the role of cAMP/PKA in stimulating changes responsible for sustaining the more persistent components of LTP, and this was mainly as a consequence of studies conducted by the Kandel group (236). For instance, it was shown that delivery of one high-frequency train (100 Hz) induced LTP that persisted for 1–3 h; this was inhibited by inhibitors of CaMKII but was not affected by PKA inhibitors or protein synthesis inhibitors. In contrast, delivery of three high-frequency trains of stimuli was shown to induce LTP that persisted for between 6 and 10 h, and this was blocked by a PKA inhibitor (236). Similarly, late-phase LTP in perforant path-granule cell synapses was shown to be inhibited by the PKA inhibitor *R*p-cAMPS and mimicked by the adenylate cyclase activator forskolin (453), while the pro-

TABLE 4. *LTP-induced signaling cascades are activated presynaptically and postsynaptically*

	Presynaptic Changes	Postsynaptic Changes
CaMKII	Increased CaMKII phosphorylation of synapsin I (175, 449) and MAP2 (175) with LTP	CaMK inhibitors block LTP (369, 373) Injection of Ca^{2+}-independent CaMKII blocks LTP (220, 337, 494) Injection of constitutively active CaMKII induces LTP (337, 494)
cAMP	LTP activates PKA presynaptically (615) Inhibition of PKA presynaptically blocks LTP (330)	Inhibition of cAMP blocks LTP (236, 476, 477) Expression of R(AB) inhibits LTP (3) Forskolin enhances LTP (453) LTP activates PKA postsynaptically (248, 520)
Tyrosine kinase	Phosphorylation of substrates (synapsin, PLC-γ, TrkA, TrkB) increased with LTP (198, 366, 396, 436) Genistein inhibits LTP by acting presynaptically (90)	Phosphorylation of substrates (NR2B) increased with LTP (528, 531) Inhibition of tyrosine kinase blocks LTP (239, 465) LTP enhances phosphorylation of CAKbeta/Pyk2 (239) Src activation accompanies LTP; Src inhibition blocks LTP (349) Fyn knockouts exhibit impaired LTP (205)
ERK	Inhibition of ERK blocks LTP (397) LTP enhances ERK activation presynaptically (90, 198, 199, 366, 397) ERK modulates LTP-associated release (90, 198, 199, 366)	Inhibition of ERK blocks LTP and signaling postsynaptically (123, 151) LTP enhances ERK activation (123, 248) ERK substrates are activated following LTP (9, 123, 248)
CREB	LTP activates CREB presynaptically (198)	LTP and CREB activation inhibited in tandem (123, 247, 554) LTP is blocked in CREB knockout mice (74) LTP increases CRE-mediated gene expression (247)
PI 3-K	LTP activates PI 3-K (282) PI 3-K inhibitors block LTP and LTP-associated signaling presynaptically (282)	PI 3-K inhibitors block LTP (541)
PKC	LTP stimulates PKC (394) LTP stimulates phosphorylation of PKC substrates (408, 506)	Inhibition of PKC blocks LTP (369, 373) LTP is associated with activation of PKC (331) LTP stimulates phosphorylation of PKC substrates (506, 578)
Protein synthesis	LTP in DG stimulates protein synthesis in EC (90, 198, 285) LTP enhances synthesis of synaptic vesicle proteins (359) Protein synthesis inhibitors block LTP and presynaptic signaling (435) LTP induces presynaptic morphological changes (25, 79, 413)	LTP stimulates protein synthesis postsynaptically (450, 480) Protein synthesis inhibitors block LTP (474, 587) LTP induces postsynaptic morphological changes (79, 126, 157, 188, 190, 555)

CaMKII, calcium/calmodulin kinase II; PI 3-K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PKA, protein kinase A; PLC-γ, phospholipase C-γ. Reference numbers are given in parentheses.

tein synthesis inhibitor emetine exerted the same effect as *R*p-cAMPS (453). This latter observation, as well as earlier observations which pinpointed the coincident timing of the effects of protein synthesis inhibitors and PKA inhibitors, suggested that the effects might be coupled and therefore led to the proposal that the primary effect of PKA was to stimulate protein synthesis. These findings were backed up by observations made in transgenic mice that express R(AB), an inhibitory form of the regulatory subunit of PKA. In these mice, in which PKA activity is markedly reduced, L-LTP was decreased in area CA1, but no effect on the early phase of LTP was observed (3). However, some evidence has suggested that PKA may also play a role in early LTP. For example, PKA was transiently activated 2 and 10 min after induction of LTP in CA1 of the hippocampus, but there was no evidence of a persistent change, suggesting that its role was confined to earlier, rather than later, events (520); it was proposed that this was a consequence of NMDA receptor activation and subsequent activation of calmodulin-dependent adenylyl cyclase (649). A role for PKA in early LTP was also proposed by Otmakhova et al. (477) on the strength of their observation that application of the PKA inhibitor H-89 suppressed the early LTP induced by a single tetanus and that LTP induced by a pairing protocol was decreased by intracellular perfusion of the peptide PKA inhibitor PKI(6—22) amide.

It had been assumed that the primary, and possibly sole, action of cAMP is to activate PKA, but a recent report requires this idea to be revisited. Perfusion of the cAMP analog *R*p-cAMPS into CA1 pyramidal cells after induction of LTP decreased the amplitude of the synaptic response in a dose-dependent manner, and the expectation was that this effect was due to its reported inhibitory action on PKA. However, the effect was not mimicked by a specific PKA inhibitor, which suggested a novel action of cAMP (476); these authors proposed that the rapid cAMP-dependent stimulation of the BDNF receptor TrkB may lead to BDNF-dependent synaptic potentiation in

CA1 which has been reported by several groups (see below; Ref. 486).

Transgenic mice in which PKA activity is decreased [because they express R(AB); see above], and which exhibited an impairment in L-LTP, also exhibited deficits in spatial memory, indicating that PKA plays a critical role in the consolidation of at least this form of memory (3). In support of a requirement for PKA activation in other forms of memory, it was demonstrated that long-term, but not short-term, contextual fear memory was also impaired in these mice. Consistently, activation of PKA was shown to accompany contextual fear conditioning while *R*p-cAMPS inhibits both LTP in amygdala and long-term contextual fear memory (547–549). Similarly, investigation of L-LTP in the cortico-amygdala and the thalamo-amygdala pathways revealed the predicted dependence on gene expression and on new protein synthesis; these changes were mediated by activation of PKA as demonstrated by the ability of forskolin to induce LTP in both pathways (238). Interestingly, mice that were maintained in an enriched environment and exhibited enhanced LTP also showed improved memory for contextual, but not cued, fear conditioning. These data suggest that exposure of mice to an enriched environment may alter signaling through PKA and consequently may modulate synaptic plasticity (144).

The dependence of different forms of plasticity on cAMP/PKA is a recurring and unifying theme. For instance, the plasticity induced in the visual cortex as a consequence of monocular deprivation has been shown to be inhibited by the PKA inhibitor *R*p-8-Cl-cAMPS (52), while a role for cAMP has been identified in experience-dependent synaptic modification in the somatosensory cortex (1). The reliance of various forms of synaptic plasticity on cAMP/PKA-induced cell signaling cascades also transcends the species. Thus long-term facilitation in *Aplysia* has been shown to be PKA dependent (55) while PKA activation has been linked with learning/memory in *Drosophila* (121), with context signal learning in the crab (338) and with associative learning in honeybees (438).

B. ERK

Among the downstream consequences of an increase in cAMP concentration is activation of the mitogen-activated protein kinase (MAPK/ERK); in the case of *Aplysia*, increased intracellular cAMP triggered nuclear translocation of MAPK (381), while cAMP also activated ERK in hippocampus (248). It has recently been shown that this effect in hippocampus may be mediated through cAMP-stimulation of TrkB, which in turn activates ERK (486). Consistently, PKA activation by forskolin was shown to strongly activate ERK2 in hippocampal area CA1 while its effect on ERK1 was slight (9). However, it has become clear in the past 10 years or so that ERK activation can be stimulated in

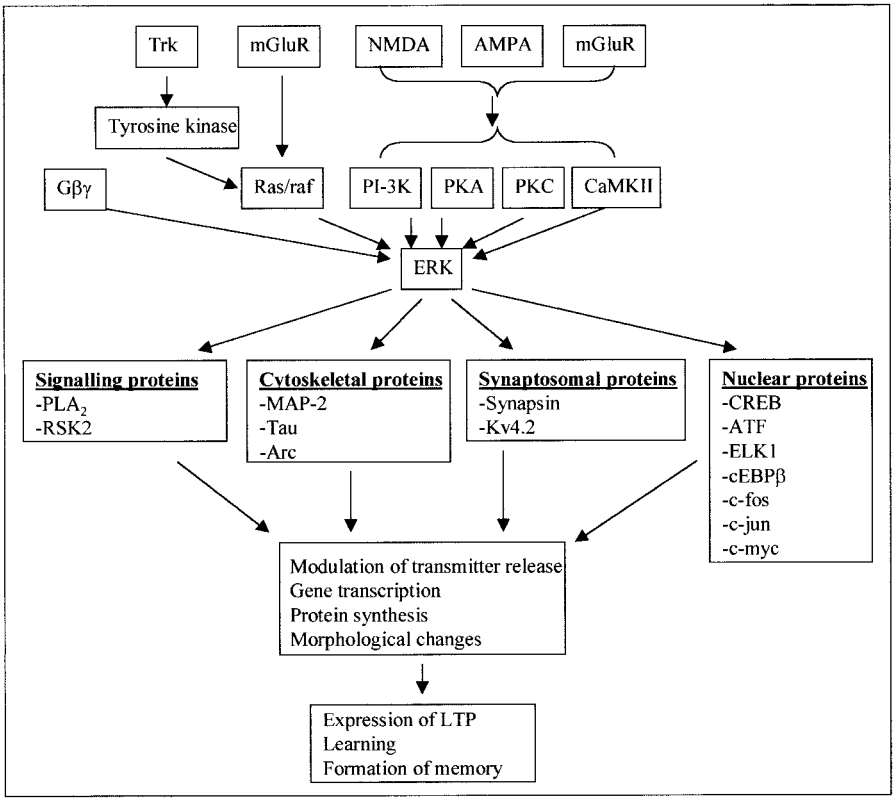

FIG. 2. ERK appears to act as a point of convergence for several signaling cascades. The multiple and varied substrates of ERK predict the array of changes that follow its activation (see text for details). PLA_2, phospholipase A_2; PKA, protein kinase A; PKC, protein kinase C; PI-3K, phosphatidylinositol 3-kinase.

many ways and can exert numerous effects because of its multiple substrate proteins (see Fig. 2 and below).

The important role of ERK in expression of LTP was first underscored by the finding that its inhibition resulted in suppression of LTP in CA1 (151, 248) and dentate gyrus (397). Consistently, it was shown that induction of LTP in the dentate gyrus in vivo led to rapid phosphorylation of MAPK/ERK (123, 151, 397; Fig. 3). ERK activation has been shown to be involved in both early- and late-phase hippocampal LTP; thus pretreatment with the MEK inhibitor PD98059 exerted an inhibitory effect on the early and later responses to tetanic stimulation (397; Fig. 3). It was proposed that this may be due to ERK-stimulated phosphorylation of potassium channels or synapsin I. To explain the rapid effect of ERK, attention focused on the finding that the potassium channel Kv4.2 is one of its substrate proteins. It seems likely that ERK regulation of Kv4.2 activation plays an important role in LTP; specifically a decrease in voltage-dependent activation of Kv4.2 would lead to increased excitability, enhancing LTP (9, 596). Synapsin I has been identified as a substrate for ERK (270, 384) as well as for cAMP-dependent kinase and CaMKII (207), and its phosphorylation by ERK has been shown to reduce synapsin-actin bundling, an action which is considered to induce vesicle movement to the active zone, increasing the likelihood of vesicle fusion (207). One expected consequence of this is an increase in transmitter release; consistently, it has been shown that KCl-

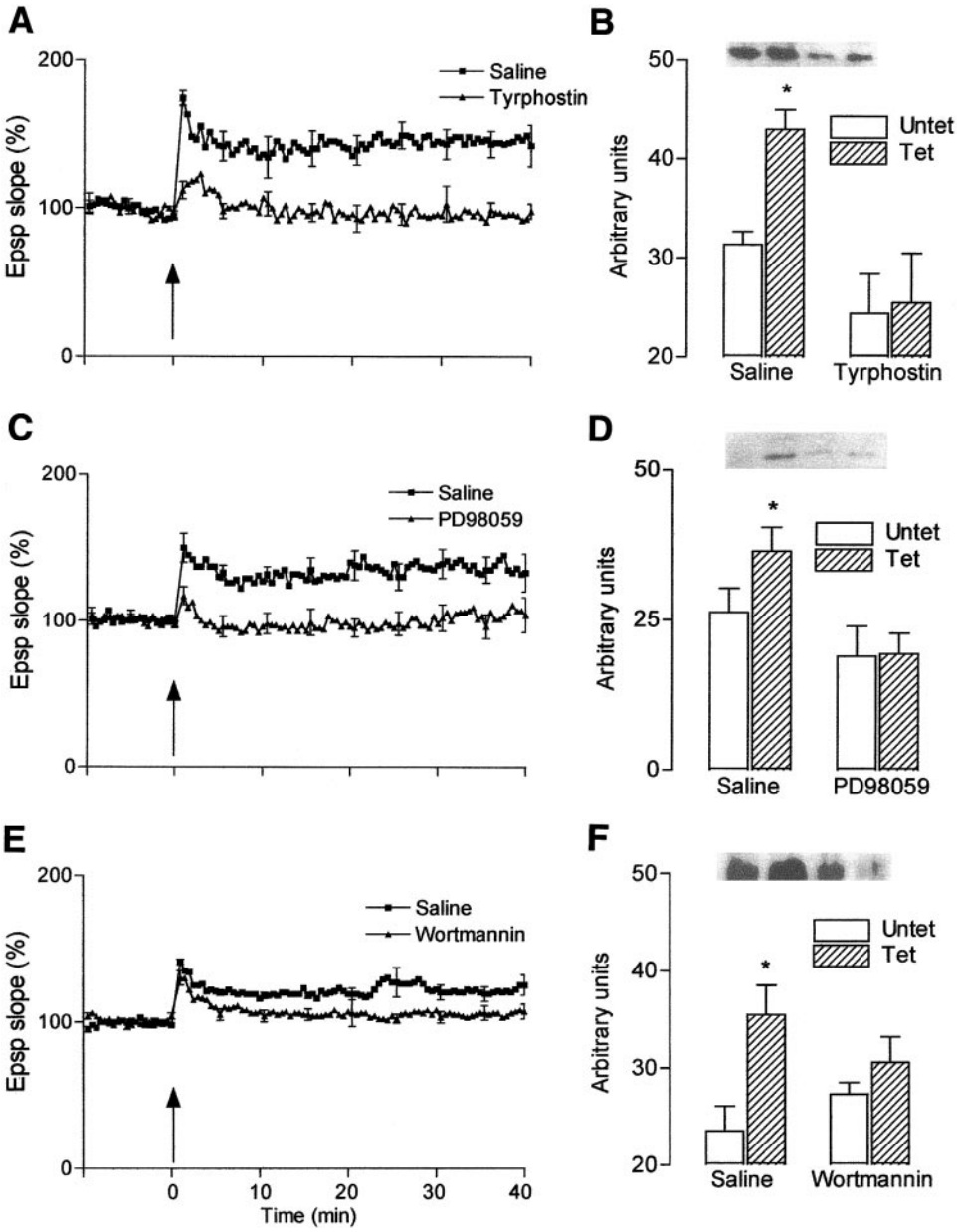

FIG. 3. Long-term potentiation (LTP) in perforant path-granule cell synapses in urethane-anesthetized rats was inhibited by the Trk inhibitor tyrphostin AG879 (*A*), the MEK inhibitor PD98059 (*B*), and the PI 3-kinase inhibitor wortmannin (*C*). Whereas ERK activation was significantly enhanced in synaptosomes prepared from tetanized dentate gyrus obtained from saline-treated rats [$P < 0.05$; ANOVA; $n = 6$; compare *lane 2* (tetanized) with *lane 1* (untetanized) on the sample immunoblot], treatment with either tyrphostin AG879 (*B*) or PD98059 (*D*) inhibited this effect (compare *lanes 3* and *4*). PI 3-kinase activation was also significantly enhanced in synaptosomes prepared from tetanized dentate gyrus obtained from saline-treated rats [$P < 0.05$; ANOVA; $n = 6$; compare *lane 2* (tetanized) with *lane 1* (untetanized) on the sample immunoblot]. Treatment with wortmannin (*F*) inhibited this effect (compare *lanes 3* and *4* on the sample immunoblot). EPSP, excitatory postsynaptic potential.

stimulated release of glutamate in dentate gyrus is inhibited by PD98059 (198, 199) and, in the context of LTP, it is interesting to note that intracerebroventricular injection of PD98059 resulted in inhibition of LTP in perforant path granule cell synapses and inhibition of the associated enhancement of glutamate release (397). A further interesting parallel is that in aged rats, which exhibit an impairment in LTP, ERK activation is attenuated and glutamate release is markedly decreased (397).

In addition to its role in hippocampal LTP, activation of the ERK/MAPK cascade is also required for expression of LTP at the amygdalar inputs into the insular cortex (266), and like CaMKII, activation of ERK has been shown to be increased after contextual fear conditioning (14, 28). With the use of conditioned taste aversion as a model for gustatory memory, it was established that increased ERK activation in the insular cortex was a component part of the molecular changes that underpinned taste aversion (56). In a striking parallel between memory and LTP, it was found that inhibition of ERK blocked both gustatory memory and LTP in insular cortex (266, 529). Like LTP in the insular cortex, LTP in visual cortex has been shown to be dependent on activation of ERK (139).

There is a great deal of evidence indicating that ERK activation plays a role in long-term memory and therefore predictably ERK inhibition profoundly affects memory. Thus it has been demonstrated that ERK inhibitors inhibit long-term, rather than short-term, memory (636), and this is consistent with the finding that ERK activation modulates gene expression and consequently stimulates protein synthesis. ERK inhibition has not been shown to impair acquisition, but it blocks the formation of long-term spatial memory (66). This was later confirmed using another ERK inhibitor, SL327, which attenuated both cue learning and water maze learning in mice (558). Consistent with a role for activation of ERK in the entorhinal cortex in spatial learning is the finding that infusion of PD98059 into the entorhinal cortex immediately after training resulted in a deficit in retention test 48 h later; interestingly, this deficit was prevented by pretraining (222). ERK activation has also been implicated in conditional taste aversion where infusion of PD98059 attenuated the response (56). Thus, although there is general agreement that long-term memory requires ERK activation, it is not yet clear which cells exhibit an increase in ERK activation after training. One group reported that ERK activation was enhanced in the pyramidal neurons of the CA1/CA2 in dorsal hippocampus of rats after training in a spatial learning task, but no significant increase was detected in CA3 or dentate gyrus (66). Our recent data indicated that ERK activation was increased in preparations of whole hippocampus obtained from rats that underwent training in the Morris water maze (199).

The argument for a role for ERK activation in learning/memory is consolidated by the fact that its involvement has been shown in forms of learning other than spatial learning. For instance, phosphorylation of ERK in hippocampus was increased in an NMDA receptor-dependent fashion, 1 h after contextual fear conditioning (28); this was coupled with the predicted observation that ERK inhibition blocked fear conditioning (28, 558). It was shown that while treatment with PD98059 or anisomycin impaired long-term memory, short-term memory remained intact (548). Similarly, gustatory memory is associated with activation of ERK (56). These observations illustrate a role for ERK activation in a variety of models of memory, and this recurrent theme has recently been extended to inhibitory avoidance learning (635, 636). The theme also extends across species, since ERK activation is essential for learned responses in *Aplysia*. Thus presentation of a single brief noxious stimulus to *Aplysia* results in enhancement of the defensive withdrawal reflex lasting several minutes. This behavioral plasticity involves presynaptic facilitation of synaptic transmission and is due to cAMP-dependent protein phosphorylation, triggered by 5-hydroxytryptamine (5-HT) release. Consistently, application of 5-HT can lead to short- or long-term retention of a learned defensive response; long-term changes are dependent on protein synthesis and involve structural changes at the synapses between the sensory neurons and motoneurons. Recent evidence has suggested that ERK activation is a key player in transduction of signals to gene transcription (298), and it has been shown that inhibition of ERK prevents long-term facilitation of sensory neurons to motoneuron synaptic signals (381) and consistently, inhibition by either anti-ERK antibodies or PD98059 blocked long-term facilitation (416). Translocation of ERK to the nucleus has been identified as one step in transduction of the signal; interestingly, long-term facilitation in *Aplysia* is associated with translocation of an ERK homolog to the nucleus of presynaptic sensory neurons in a 5-HT-driven and cAMP-dependent manner (381). Consistent with a specific role for ERK activation in long-term but not short-term memory is the finding that translocation does not occur when transient facilitation is induced in *Aplysia* (381).

The downstream consequences of ERK activation are wide ranging; ERK substrates include the cytoskeletal proteins MAP-2 and Tau; the nuclear proteins c-Myc, c-*fos*, and c-*jun*; Elk-1; CREB; C/EBPβ (CREB/Elk binding protein); and ATF-2 and the signaling proteins phospholipase A_2 and RSK (ribosomal S6 kinase). Other substrate proteins are the potassium channel Kv4.2 and synapsin I as described above.

The long-term effects of ERK activation involve translation and transcription (170, 612), which requires ERK translocation to the nucleus (68). The LTP-associated parallel increases in activation of ERK, CREB, and Elk-1 have been shown to be accompanied by upregulation of the immediate early gene zif268; this was blocked

by the MEK inhibitor SL327, indicating a critical role for ERK in gene activation (123). Consistently, a rapid and reproducible upregulation of zif268 mRNA has been reported in granule cells of the dentate gyrus (108, 647), and this was attenuated when LTP was inhibited by PD98059 (which inhibited LTP); the changes in Homer closely paralleled those in zif268 (123, 530). These changes probably preface the increase in protein synthesis, which has been clearly linked with ERK and CREB activation, for example, after LTP in dentate gyrus (198).

Of the several downstream effectors of ERK, CREB in particular has received a great deal of attention, probably since it has been shown to be also activated by other upstream activators (see below). ERK activation leads to activation of CREB indirectly by coupling to RSK2, since phosphorylation of CREB at Ser-133 cannot be achieved by ERK. RSK2 and other kinases recruit the CREB binding protein (CBP), which is the first step in gene transcription. Since the early reports (451, 454), it has been shown many times that CREB activation is a consequence of ERK activation. In the context of LTP, initial studies showed that mutant mice lacking CREB isoforms α and δ exhibit attenuated LTP (74). It was subsequently reported that CRE-mediated transcription was increased in response to LTP induction in area CA1 (247), while increased CREB phosphorylation accompanied tetanus-induced LTP and BDNF-induced potentiation in dentate gyrus (198, 347, 387, 554, 657). Inhibitors of ERK, which blocked LTP, also blocked CREB activation (123, 198, 248, 554). Consistently, in CRE-LacZ transgenic mice, LTP in CA1 was coupled with upregulation of LacZ expression (247), while LTP is associated with an increase in CREB-driven gene expression. It is significant that LTP-induced increases in CREB phosphorylation were observed both presynaptically and postsynaptically. Thus when LTP was induced in perforant path-granule cell synapses, CREB activation in the dentate gyrus was observed 24 h later while it was observed less than 2 h later in entorhinal cortex (199). Interestingly, BDNF-induced LTP was associated with enhanced CREB activation in hippocampus after 15 min, but this change in CREB was not observed at 3 h, suggesting that, at least in this case, there is biphasic activation of CREB (656); this early change in CREB activation was also observed in dentate gyrus after tetanus-induced LTP (123).

ERK may be a point of convergence of signals from several kinases activated as a consequence of LTP induction (248, 519). CREB activation may also represent a point of convergence since it, like ERK, has been shown to be activated downstream of PKA, PKC, and CaMKII; it has yet to be established whether ERK acts as a mediator in all cases. In contrast to ERK, which utilizes RSK2 to activate CREB, phosphorylation on Ser-133 by PKA can occur directly. However, U0126 has been shown to block CREB phosphorylation in response to forskolin application (347, 519), indicating a mediating role for ERK at least in some cases. Recent evidence has revealed that PKC also converges on CREB and that CREB activation by PKC is mediated by ERK (519).

C. Phosphatidyinositol 3-Kinase

It has become clear in recent years that ERK activation can also be affected by phosphatidylinositol 3-kinase (PI 3-kinase), which was identified several years ago as a substrate for tyrosine kinase (see Ref. 172). The idea that activation of tyrosine kinases was important for expression of LTP was suggested by the finding that kinase inhibitors prevented expression of LTP in CA1 and dentate gyrus (436, 465) and that mice, in which the nonreceptor tyrosine kinase fyn was knocked out, were unable to sustain LTP (205). These data were consolidated by the findings that tyrosine phosphorylation of several substrates was increased after induction of LTP; these included phospholipase C (PLC)-γ (396), synaptophysin (436), the α-subunit of voltage-activated calcium channels (90), TrkA (366), TrkB (198), and the 2B subunit of the NMDA receptor (528, 531). ERK is also a substrate for tyrosine kinase, but its activation requires dual phosphorylation on tyrosine and threonine residues. A series of phosphorylation steps leads to activation of MEK, which dually phosphorylates, and thereby fully activates, ERK. Activation of MEK can be achieved by a number of upstream signaling events. For example, activation of metabotropic glutamate receptors leads to activation of the ras/MEK/ERK cascade (161, 301), and similarly, certain isoforms of PKC (203) and the $\beta\gamma$-subunit of heterotrimeric G proteins (625) can also contribute to its activation. At least two tyrosine kinase substrates, raf (379) and PI 3-kinase (140), can also lead to phosphorylation of MEK.

It is interesting, therefore, that LTP in dentate gyrus (282) and CA1 (541) were both inhibited by PI 3-kinase inhibitors, while induction of LTP was associated with kinase activation (Fig. 3). In the case of the dentate gyrus, wortmannin inhibited the LTP-associated increase in glutamate release, and it also inhibited depolarization-induced glutamate release in vitro (282). Sanna et al. (541) concluded on the basis of recovery of LTP after washout of the inhibitor, that PI 3-kinase activity was required for early expression of LTP rather than for its longer term maintenance. This is not the conclusion drawn from experiments that were conducted in the amygdala. In this case, activation of PI 3-kinase was shown to be increased in amygdala of rats that underwent fear conditioning, and this was paralleled by a similar increase in kinase activation after induction of LTP (329). However, these authors also reported that PI 3-kinase inhibitors blocked tetanus-induced LTP and interfered with long-term fear memory,

but left short-term memory intact. In contrast, both short-term and long-term memory were shown to be affected by PI 3-kinase inhibition when assessed in a step-down inhibitory avoidance training paradigm, and it was concluded that activation of PI 3-kinase in hippocampus was necessary for memory acquisition, consolidation, and retrieval of step-down inhibitory avoidance in rats (45). Despite the fact that these studies have identified a role for PI 3-kinase in a few forms of synaptic plasticity, details of the events leading to its activation and the changes which occur downstream of its activation remain to be systematically elucidated. One group has initiated a study of the consequences of PI 3-kinase activation in synaptic plasticity in amygdala and has reported that inhibition of PI 3-kinase blocked LTP-associated activation of ERK and CREB, suggesting that PI 3-kinase modulates synaptic plasticity by an action upstream of ERK activation (329). Meanwhile, there has also been some progress in assessing changes linked with PI 3-kinase activation in vitro. Significantly AMPA- and NMDA-dependent activation of ERK is PI 3-kinase dependent, and glutamate-induced activation of striatal neurons has been shown to induce PI 3-kinase-dependent phosphorylation of Akt and CREB (492).

D. The Consequences of CREB Activation

Activation of CREB has been identified as a critically important transcription factor in memory formation. Like ERK activation, its role has been described in several forms of learning and memory and in a number of species. For instance, CREB-dependent transcription has been associated with long-term memory in *Drosophila* and *Aplysia* as well as in mice and rats (89, 569). Indeed, among the earliest studies were the reports that CREB activation was essential for long-term facilitation in *Aplysia* and for long-term memory in *Drosophilia* (74, 381). At about this time it was also shown that mice with a hypomorphic CREB allele, generated by homologous recombination, displayed deficits in water maze learning and fear conditioning, indicating similar responses in mammals (242). Since then a few studies have confirmed this observation. Thus CREB phosphorylation was shown to be increased in hippocampus and entorhinal cortex of rats that were trained in a Morris water maze (199), while contextual fear learning has also been shown to stimulate the phosphorylation of CREB in the hippocampus of mice (248). Local microinjection of phosphorothioate-modified oligodeoxynucleotides antisense to CREB into the rat amygdala impaired conditioned taste aversion memory when tested 3–5 days later (303), and similarly intrahippocampal injections resulted in impairment in long-term spatial memory (210). In contrast, environmental enrichment, which resulted in improved performance in the Morris water maze, was paralleled by increased CREB immunoreactivity in the hippocampus (642).

Induction of LTP has been associated with rapid and transient activation of several immediate early genes (IEGs), which parallels increases in protein synthesis and CREB phosphorylation; consistently, agents that inhibit LTP and CREB activation also inhibit protein synthesis (198, 366) as well as transcription of certain IEGs (656). The close coupling between CREB phosphorylation and protein synthesis was also identified by the finding that CREB activation is an essential step in the cascade leading to the generation of new dendritic spines, the primary targets of excitatory synaptic inputs associated with long-term morphological modifications seen during LTP (440). CREB activation has also been shown to be essential for BDNF-induced transcription (160) and plays a key role in BDNF-induced potentiation (see below).

E. Activation of IEGs and Late-Response Genes in LTP

The first evidence of activation of IEGs in LTP was reported in the early 1990s. In these studies it was shown that induction of LTP in dentate gyrus in anesthetized rats was associated with a consistent increase in expression of zif268 but not in c-*fos* (516, 647), although increases in c-*fos*-related genes, c-*jun*, junB, and junD were also described (6). In the awake rat, it was established that rapid, transient increases in c-*jun* and jun-B mRNA and protein and in Fos-related protein were associated with LTP in the dentate gyrus and that these changes were NMDA receptor dependent. A more delayed and persistent increase in jun-D mRNA and protein was observed (124). Although several changes in IEGs have been described, perhaps the most consistent LTP-associated changes have been shown to occur in zif268 (see below).

Recent attention has focused on analysis of changes in activity-regulated cytoskeleton-associated protein (Arc) in LTP. Arc is upregulated at the mRNA and protein levels by synaptic activity, and while this is known to be NMDA receptor dependent, the details of the signaling events leading to its induction remain unclear (332, 352, 591). Arc mRNA is delivered to dendrites and translated within minutes after tetanic stimulation, and Arc protein is locally translated. Because Arc protein binds to actin, it has been proposed that it participates in cytoskeletal restructuring after synaptic activation, and therefore, one challenge is to assess whether restructuring actually depends on upregulation of Arc.

Consistent with the observed LTP-associated change in Arc, disruption of Arc by antisense oligonucleotides inhibits LTP and also long-term spatial memory (211). Interestingly, only long-term changes were affected, so induction of LTP and short-term memory were intact.

Recent data have revealed that BDNF-induced potentiation is coupled with Arc activation and that this is mediated by phosphorylation of ERK (656). It has been shown in an in vitro study that BDNF upregulates Arc synthesis and activates CaMKII in synaptoneurosomes in an NMDA-dependent manner (657). Interestingly, although this preparation contains both presynaptic and postsynaptic elements, mRNA for both Arc and CaMKII were found in purified synaptosomes, suggesting that, in addition to its effects in the postsynaptic neuron, Arc may contribute to morphological changes that have been observed in the presynaptic terminal after induction of LTP. Although Arc expression and CaMKII activity are stimulated by similar events and although Arc activation modulates CaMKII (211), the specific importance of these observations in the context of LTP or memory remains unclear.

IEGs are also described as early-response genes, and they act as transcription factors to induce late-response genes. After translation in the cytoplasm, early-response gene products bind to regulatory sites on DNA in the nucleus, stimulating transcription of late-response genes. Protein products of late-response genes may be structural proteins, enzymes, ion channels, or neurotransmitters, which are involved in neuronal growth and neuronal plasticity. Receptors are another likely protein product, and there is specific evidence that L-LTP is associated with synthesis of AMPA receptors (450).

E-LTP has a decay time constant of ~2 h, whereas L-LTP can be divided into that which is protein synthesis dependent, with a decay time constant of ~4 days (LTP2), and the component which is dependent on new transcription and translation, with a decay time constant of ~23 days (LTP3; Ref. 7). The latter is associated with increased levels of certain transcription factors like zif268 (also called Egr1), Egr2, and Egr3 (516, 645, 654) and AP-1, c-*jun*, and jun-B (108). In the case of zif268, which is perhaps the most studied IEG in relation to LTP, one gene product was identified as a nerve growth factor response gene product in PC12 cells (417), which has been shown to stimulate cell growth and differentiation (185).

Induction of LTP in dentate gyrus leads to a rapid and robust NMDA-dependent transcription of zif268 (108, 647), and although the change occurs almost immediately, expression of zif268 mRNA has been identified as a critical element in stimulating protein synthesis on which consolidation of LTP depends (6). Once stimulated, zif268 protein binds to its response element, and this binding has been detected after induction of LTP (644). Interestingly, it has become clear that LTP, induced in adult visual cortex by stimulation of the lateral geniculate nucleus (229) and in insular cortex by stimulation of the basolateral amygdala (266), is associated with an increase in zif268 immunoreactivity, although there is no evidence of a similar response in CA1 after stimulation of Schaffer collaterals (166).

Results from a recent study using zif268 knockout mice demonstrated that this gene is required for both late LTP as measured 2 and 3 days after high-frequency stimulation (HFS) and hippocampal-dependent long-term memory (75, 267). While LTP in wild-type and mutant mice was similar in the first hour after tetanic stimulation in anesthetized and freely moving animals, subsequent analysis, after 24 and 48 h, in the freely moving animals revealed an absence of LTP in mutant mice; whereas induction of zif268 was observed in wild-type mice, it was absent in mutant mice. These findings were closely paralleled by data obtained from analysis of spatial memory; thus short-term memory was intact in mutant mice but long-term memory was severely impaired. Interestingly, behavioral impairments extended beyond changes in spatial memory, since both object recognition and conditioned taste aversion were similarly affected (75, 267).

Like zif268, induction of Arc (see above) and junD have been associated with L-LTP (241). Indeed, this group has systematically assessed the sequential changes in inducible transcription factors after paradigms that induce LTP1, LTP2, and LTP3 and have concluded that expression of these factors does not correlate well with the extent of change in early LTP but rather with consolidation and longevity of LTP. Specifically it was shown that robust expression of zif268 and Egr2 was observed with paradigms that resulted in LTP3, whereas less robust expression was observed with paradigms that resulted in LTP2 (241); this is consistent with the findings of the Laroche group (see above).

F. Protein Synthesis and LTP

Evidence suggests that the switch from early- to late-phase LTP requires gene expression and protein synthesis, with studies from several laboratories demonstrating that tetanus-induced potentiation of the synaptic response in CA1 and dentate gyrus was relatively short-lived in animals that were injected with protein synthesis inhibitors (300, 435, 474, 475, 587). However, actinomycin D, an inhibitor of mRNA synthesis, exerted no significant effect during the first 3 h after tetanus (168, 474), although an inhibitory effect was observed after ~5 h (168), suggesting a dependence on transcription and translation at this time. Interestingly, there was evidence of newly synthesized proteins in the extracellular medium 3 h after induction of LTP (155), while increased synthesis of presynaptically located proteins was also reported within this time frame (359). Similar temporally distinct phases were distinguished with respect to learning in 1980 when it was reported that intrahippocampal injection of the protein synthesis inhibitor anisomycin inhibited retention

in a brightness discrimination task but that the inhibition only occurred if the drug was administered before training or several hours after training; injection of anisomycin shortly after training failed to affect retention (206). These data indicate that activation of the cellular machinery that leads to protein synthesis and hence to the retention of the task occurs in the minutes immediately after training and that a further "wave" of cell activity occurs later.

It is likely that the increase in protein synthesis that accompanies LTP contributes to the establishment of the morphological changes that have been reported, for example, the increases in postsynaptic surface area (126), spine number (e.g., Refs. 95, 317), and spine area (157). LTP has also been shown to increase the number of large spines (126) and axospinous perforated synapses (188, 190, 555) and perforated synaptic densities with larger apposition zones between pre- and postsynaptic structures (79). Changes in distribution (25) and numbers (413) of synaptic vesicles and changes in synaptic curvature (127) have also been reported. These observations support the view that morphological changes occur on both sides of the synapse (149, 334), and this idea is consolidated by data from biochemical analysis. For example, Nayak et al. (449) observed that late-phase LTP can be supported in CA1 minislices in which the cell bodies of presynaptic Schaffer collaterals are removed and that this was accompanied by an increase in synthesis of AMPA receptor subunits; thus protein synthesis occurred in the postsynaptic cell, and LTP was sustained in the absence of protein synthesis in the presynaptic cell. Further evidence that protein synthesis occurred in the postsynaptic neurons after LTP in Schaffer collateral-CA1 synapses was provided by the observation that potentiation of the synaptic response was accompanied by an early increase in the concentration of the α-subunit of CaMKII in dendrites and that this increase was blocked by anisomycin (480). Similarly, neurotrophin-induced synaptic potentiation has been coupled with increased protein synthesis (273), and it was suggested that, in these two cases, synthesis occurred in dendritic spines in which polyribosomes have been located (616). On the other hand, LTP in perforant path-granule cell synapses has been shown to be accompanied by increased protein synthesis in both granule cells (M. Casey and M. A. Lynch, unpublished data) and entorhinal cortex (285, 435) and that among the proteins synthesized after tetanic stimulation were presynaptic proteins, synapsin, synaptophysin, and synaptotagmin (359). Further evidence of increased protein synthesis in presynaptic cells was described in cultured CA1 and CA3; here an increase in the number of active presynaptic terminals (assessed using the fluorescent dye FM 1–43) accompanied a form of synaptic plasticity induced by a membrane-permeable analog of cAMP (*S*p-cAMPS; Ref. 362). Significantly this effect was blocked by anisomycin, indicating that the change was dependent on protein synthesis. The authors speculated that these observations were consistent with recruitment of previously silent synapses. Further indirect evidence suggesting that protein turnover is increased presynaptically includes the observation that there is enhanced vesicular recycling after potentiation of hippocampal synaptic responses in models that resembled LTP by two independent groups (371, 534). It might be speculated that changes of this nature are necessary to support the persistent increase in glutamate release that has been consistently shown to accompany LTP, at least in perforant path-granule cell synapses (62, 85, 392, 397–400).

One question that remains to be addressed is how does synaptic activity leading to LTP trigger translation in neurons? One possibility is that it triggers local dendritic protein synthesis, which is required for maintenance of BDNF-induced potentiation (590, 603; see below). One protein that plays a role in initiation of translation is mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that regulates the activity of proteins that bind to eukaryotic initiation factor-4E (4E-BPs). Phosphorylation of 4E-BPs by mTOR allows these proteins to dissociate from initiation factor-4E (eIF-4E), thereby initiating translation. mTOR, eIF-4E, and two distinct 4E-BPs have been located at dendrites and cell bodies of hippocampal neurons, but they have also been shown to colocalize with synapsin I, indicating their presence presynaptically as well as postsynaptically. Of significant interest is the finding that rapamycin, which inhibits mTOR, blocked the expression of late-phase LTP (602a).

VI. NEUROTROPHINS, LONG-TERM POTENTIATION, AND MEMORY

The first reports indicating that neurotrophins modulated LTP appeared more than a decade ago when the work of two groups demonstrated that epidermal growth factor and fibroblast growth factor enhanced LTP in CA1 (2, 608, 609). More recently, the focus of attention has been on nerve growth factor (NGF), BDNF, and neurotrophin-3 (NT-3), which bind preferentially to TrkA, TrkB, and TrkC (113, 250, 294). The first series of experiments showed that acute application of exogenous BDNF enhances synaptic transmission and induces a form of potentiation that resembles LTP in CA1 cultures (272, 563) and CA1 slices (158, 299). NT-3 was also shown to induce a similar potentiation in hippocampus (272), a finding which was replicated in isolated spinal cord (26). However, a more recent assessment of LTP in CA1 prepared from mice in which NT-3 was knocked out later in development (to avoid the lethality associated with homozygous knockouts) indicated that NT-3 was not necessary

for induction of LTP (361). NGF did not induce LTP in CA1 (272, 601), possibly because of the low TrkA density in this area, but indirect evidence suggests that NGF may play a role in expression of LTP in perforant path granule cell synapses where expression of the neurotrophin and its receptor are relatively high (182, 431). LTP was found to be impaired in dentate gyrus of genetically hypertensive (GH) rats, in which NGF concentration and Trk were decreased, while intraventricular injection of NGF reversed this deficit in LTP (281). In addition, induction of LTP in this area increased NGF mRNA expression (76, 93). While neither NGF nor NT-3 induced persistent potentiation in the visual cortex, application of BDNF enhanced the synaptic response in a dose-dependent manner (12).

The focus of attention on BDNF-induced potentiation has intensified with the finding that, in addition to its stimulatory effect in vitro, intrahippocampal infusion of BDNF into anesthetized rats leads to potentiation of the synaptic response in dentate gyrus (414). Like LTP induced by tetanic stimulation, BDNF-induced potentiation was shown to rely on NMDA receptor activation and to be ERK and CREB dependent; thus, while potentiation was associated with enhanced phosphorylation of ERK and CREB, it was inhibited by local infusion of MEK inhibitors PD98059 and U0126, and in these experiments, evidence of activation of ERK and CREB was predictably absent (415). Similarly, BDNF-induced potentiation is associated with upregulation of Arc, while both BDNF-induced potentiation and the associated increase in Arc expression were blocked by actinomycin D (415). A role for BDNF in expression of LTP has therefore been bolstered by these findings and by a great deal of indirect evidence. For example, inhibition of tyrosine kinases such as TrkB using K252a or tyrphostin AG879 blocks LTP (198, 366, 424), transgenic mice with a targeted deletion of the BDNF (299, 485) or TrkB (419) gene exhibit impaired LTP and exposure of slices to TrkB-IgG, a BDNF scavenging protein or a specific BDNF monoclonal antibody reduced LTP (99, 158). Interestingly, in BDNF knockout mice, reexpression of the BDNF gene through transfection or treatment with recombinant BDNF results in restoration of LTP (485). It has also been demonstrated that BDNF mRNA expression is increased after the induction of LTP in the CA1 region of the hippocampal slice (485) and in the granule cells of the dentate gyrus (76, 93, 142, 424). An early increase in BDNF protein (198) has been coupled with the early (30 min posttetanus) increase in mRNA in perforant path granule cell synapses (424), suggesting that BDNF protein is quickly translated and upregulated after the induction of LTP in vivo.

BDNF has been shown to act presynaptically and postsynaptically; for example, BDNF increases the frequency of miniature EPSCs and enhances paired-pulse facilitation (201), and it increases synaptic transmission in *Xenopus* nerve-muscle preparations (339, 594) and in cultured hippocampal neurons (319). Furthermore, presynaptic, but not postsynaptic, expression of *TrkB*.T_1, a COOH-terminal truncated dominant negative *TrkB* receptor, inhibited BDNF enhancement of synaptic transmission (322), while activation of *TrkB*-associated signaling enhanced neurotransmitter release from presynaptic terminals (315, 322). Consistently, we have found that incubation of synaptosomes in the presence of BDNF, which enhances phosphorylation of *TrkB*, also enhances glutamate release, and this is inhibited by K252a, suggesting that the effect is dependent on *Trk* activation (198, 199). However, BDNF increased amplitude of miniature EPSPs (319) while intracellular application of K252a blocked the BDNF-induced synaptic enhancement in cortical cultures (319). Similarly, BDNF-induced potentiation in dentate gyrus was shown to be coupled with increased activation of ERK and CREB, and these effects were considered to reflect a postsynaptic action of BDNF (415), although similar effects occur presynaptically (198).

Among the substrates that are activated following BDNF stimulation of TrkB is ERK (228, 378, 390), and BDNF-induced ERK activation has been shown to occur in dentate gyrus in vitro (198, 199) and after intrahippocampal injection of BDNF (657). In vitro experiments identified the importance of receptor activation in downstream signaling, since BDNF-induced increases in phosphorylation of both TrkB and ERK were blocked by the Trk inhibitor tyrphostin AG879 (199; Fig. 3). The important role of this kinase in expression of tetanus-induced LTP was underscored by the finding that its inhibition resulted in suppression of LTP (see above); in parallel, while intrahippocampal infusion of BDNF leads to rapid phosphorylation of ERK, infusion of ERK inhibitors blocked potentiation (657).

Increases in BDNF mRNA and protein have been recorded in hippocampus after training in a spatial learning task (199, 421) and in dentate gyrus after training in a passive avoidance test (363), paralleling the changes observed after induction of LTP. Consistently, a rapid and selective induction of BDNF expression has been reported in amygdala during hippocampus-dependent contextual learning (212). It has been shown that behavior in the water maze test is impaired in mutant mice carrying a deletion of one copy of the BDNF gene (333) or in rats that had received an intracerebroventricular infusion of anti-BDNF antibody (432). Moreover, injection of BDNF antisense oligonucleotides into the dentate gyrus impaired retention in a passive avoidance paradigm (363). Interestingly, spatial memory impairment has been linked with the decrease in BDNF concentration, which is a feature of hypoxic-ischemic insult (19, 292), while it was

also reported that aged rats, which were shown to have decreased BDNF mRNA, exhibited memory deficits (116).

Minichiello et al. (419) generated conditionally gene targeted mice, known as TrkB-CRE mutant mice, in which the knockout of the TrkB gene postsynaptically led to elimination of TrkB protein in the forebrain; these animals exhibited impairments in spatial learning and also LTP. Regression analysis revealed that an age-related decrease in TrkB mRNA in the pons predicted impaired memory performance of rats in the Morris water maze (116).

Consistent with a role for BDNF-induced ERK activation in learning/memory are the findings of several groups which indicate that certain forms of learning are associated with ERK activation (see above). Interestingly, it has been shown that training animals in the Morris water maze increased BDNF concentration in hippocampus, and this was coupled with increased BDNF release and increased ERK activation; these changes were strikingly similar to those observed after induction of LTP in dentate gyrus (199). Environmental enrichment, which increases BDNF concentration in hippocampus (243), resulted in improved performance in the Morris water maze, and this was paralleled by increased CREB immunoreactivity in the hippocampus (642). Similarly, environmental enrichment enhanced memory for contextual fear conditioning, but not cued fear conditioning, and interestingly, hippocampal slices prepared from these mice exhibited enhanced LTP in CA1 (144).

An age-related decrease in BDNF mRNA has been described (116), but other studies reported no significant difference between the expression of BDNF in the hippocampi of old and young rats (116, 309, 405), despite the fact that BDNF mRNA and protein were both decreased in other brain areas like the pons (116). An age-related increase in BDNF was reported by Katoh-Semba et al. (278), and recent experiments in this laboratory have confirmed this observation; our findings revealed that while BDNF concentration in hippocampus (M. Gooney, E. Messaondi, F. O. Maher, C. R. Bromham, and M. A. Lynch, unpublished data) and cortex (367) were increased, ERK activation was decreased. The evidence which indicated that TrkB activation was downregulated with age suggested that the primary deficit is associated with alterations in receptor function. In a recent report, it was shown that BDNF mRNA expression in the CA1 of aged rats that performed well in a spatial learning task was enhanced after training, but this increase was not observed in rats which exhibited an impairment in spatial learning and, in addition, basal expression of BDNF mRNA was lower in this group (546). Interestingly, age-related decreases in TrkB expression (116, 544), TrkB phosphorylation (Gooney et al., unpublished data), and ERK activation (235, 397, 660) have been reported, whereas ERK phosphorylation was decreased in dentate gyrus of aged rats that did not sustain LTP (397).

Hippocampal NGF concentration has also been reported to decrease with age (310), and Henrikkson et al. (225) have reported that good performance in a spatial learning task correlated with higher levels of NGF in the hippocampus of aged rats. However, this age-related decrease in NGF was not confirmed (117), and recent studies from this laboratory have indicated that although NGF concentration was decreased in hippocampus of aged rats (284), it was increased in cortex (367).

VII. SYNAPTIC PLASTICITY AND THE STRESSED BRAIN

A. Behavioral Stress

The influence of hormones on hippocampal function, particularly those secreted as a consequence of activation of the hypothalamo-pituitary-adrenal axis (HPA) mainly as a response to stress, has been acknowledged for several decades. Stress is best described as a disturbance of physiological and psychological homeostasis ultimately controlled by activity of the HPA and resulting in secretion of corticosteroids from the adrenal cortex. The hippocampus has the highest concentration of corticosterone receptors in the brain (see Ref. 391), and the profound effects of stress on hippocampal function, and in particular on learning and memory processes, have been attributed to this (for example, see Ref. 526).

Identification of the mechanisms by which stress leads to modulation of hippocampal function has been the subject of intense interest and has been regarded as an opportunity to dissect the cellular changes that accompany neuronal plasticity. An interesting, and perhaps predictable, finding is that stress levels of glucocorticoids have a profound inhibitory effect on hippocampal cell activity (598), while low levels of glucocorticoids enhance activity (264), and this pattern is repeated with respect to glucocorticoid levels and LTP. Therefore, high concentrations of circulating glucocorticoids, consistent with marked stress, inhibited LTP while low concentrations of glucocortocoids enhanced LTP (134, 133, 288, 488). Consistent with these concentration-dependent changes is the finding that spatial learning, as analyzed in an eight-arm radial maze, was attenuated after administration of high doses of corticosterone (350); similarly, placing rats into a profoundly fear-provoking environment (that also leads to high circulating concentrations of corticosteroids) impairs memory (135) and also LTP induced by primed-burst potentiation (412). Analysis of receptor activity has clarified the mechanism underlying the dose-dependent effects of glucocorticoids; thus it has been revealed that

type I receptor activation restored performance in a spatial learning task after adrenalectomy, whereas type I and type II activation, in combination, impaired performance (623).

The effect of stress on LTP has been studied by a number of groups, and most data point to an inhibitory effect of stress. For example, slices prepared from rats that were subjected to stress exhibited impaired LTP in area CA1 of the hippocampus in vitro (163, 566, 567). Similarly, it was shown that stress inhibited LTP in CA1 in the awake rat (132, 134, 652) and in dentate gyrus in the urethane-anesthetized rat (442, 629). Several groups have shown impairment in neuronal function in animals that were exposed to psychological stress. The study by Garcia et al. (184) described impairment in LTP in the CA1 region of mouse hippocampal slices after exposure to acute stress. This impairment was evident 24 h after the stress induced by restraint and tail shock, but LTP was restored 48 h later; therefore, this impairment in neuronal function was reversible and temporary. Another study noted that LTP was impaired in the dentate gyrus of hippocampal slices from rats that were restrained and exposed to tail shock every minute for 30 min; indeed, additional exposure to tail shock markedly accentuated the effect compared with animals that were just restrained (163).

Rather than exposing animals to paradigms such as psychological stress, which can be difficult to replicate and may be associated with unidentifiable variables, studies have simulated the effects of stress by treating animals with corticosterone. In one such study, the effect of a single high dose of corticosterone was shown to inhibit LTP in the dentate gyrus in the short term, but this effect was not observed after 48 h (488). To simulate long-term stress, corticosterone was administered for 21 days, and the inhibiting effect of this treatment regime persisted for 2 days after cessation of treatment (488). Similarly, in vitro experiments have revealed that corticosterone reduced LTP (17, 515). It seems reasonable to conclude, on the basis of these and other studies, that the concentration and persistence of plasma corticosteroids determine the effects on neuronal tissue, and it is assumed that stress, by increasing circulating levels of corticosterone, results in glucocorticoid receptor activation in hippocampus. This view is supported by the finding that administration of the glucocorticoid receptor agonist RU28362 prevented an LTP-inducing stimulation paradigm from inducing LTP; indeed, it resulted in LTD (487). Although an inverse relationship between circulating corticosteroid concentration and the ability of rats to sustain LTP seems to be a consistent finding, a more complex relationship between potentiation and circulating corticosteroids was identified when the effect of primed-burst stimulation was assessed, such that at low concentrations of circulating corticosteroids a direct relationship with LTP was observed and at high concentrations an inverse relationship existed (130). This accurately reflects the concentration-dependent changes in spatial memory. In addition to its effect on LTP, stress has been shown to enhance LTD in CA1 in vitro (289) and also in the awake rat (652), and in the latter case, the effect of stress has been shown to be dependent on glucocorticoid receptor activation and on protein synthesis.

The effects of stress are not confined to an increase in glucocorticoid production, and several neurohormones and neurotransmitters that are released as a consequence of stress, for example, opioids, norepinephrine, epinephrine, and vasopressin, modulate hippocampal function. In the past few years it has emerged that the proinflammatory cytokine interleukin-1β (IL-1β) may be a key mediator of stress, and evidence suggests that many forms of behavioral stress (although not predator stress, Ref. 498) increase brain IL-1β expression (442, 452, 504). IL-1β is known to stimulate secretion of corticotrophin releasing factor from the hypothalamus (542), and it has been reported that intrahippocampal administration of IL-1β resulted in activation of the HPA (409), confirming the observation that the hippocampus can modulate hypothalamo-pituitary function (306). These data present the possibility that increased IL-1β concentration in hippocampus might contribute to the stress-associated increase in circulating corticosteroids, while it has also been postulated that IL-1β may trigger some of the stress-induced changes in monoaminergic function (145). Further evidence that lends support to this idea has been obtained from analysis of changes in the aged animal. Thus the age-related increase in IL-1β concentration in hippocampus (441, 442) is correlated with increased plasma levels of corticosterone (306, 442), with an impairment in LTP (67, 306-308, 442; Fig. 4) and with poor performance in a variety of hippocampal-dependent learning tasks (193, 501).

B. Oxidative Stress

A negative effect of reactive oxygen species (ROS) on synaptic plasticity has been consistently described; for example, H_2O_2 is known to inhibit LTP in CA1 in vitro (29, 490) and dentate gyrus in vivo (Fig. 4), where the effect is associated with increased ROS (283, 355). Indeed, a negative correlation between ROS concentration in hippocampus and ability of rats to sustain LTP has been described (355), and therefore, the finding that isolation stress that was associated with attenuated LTP in dentate gyrus (442, 629) led to an increase in accumulation of ROS

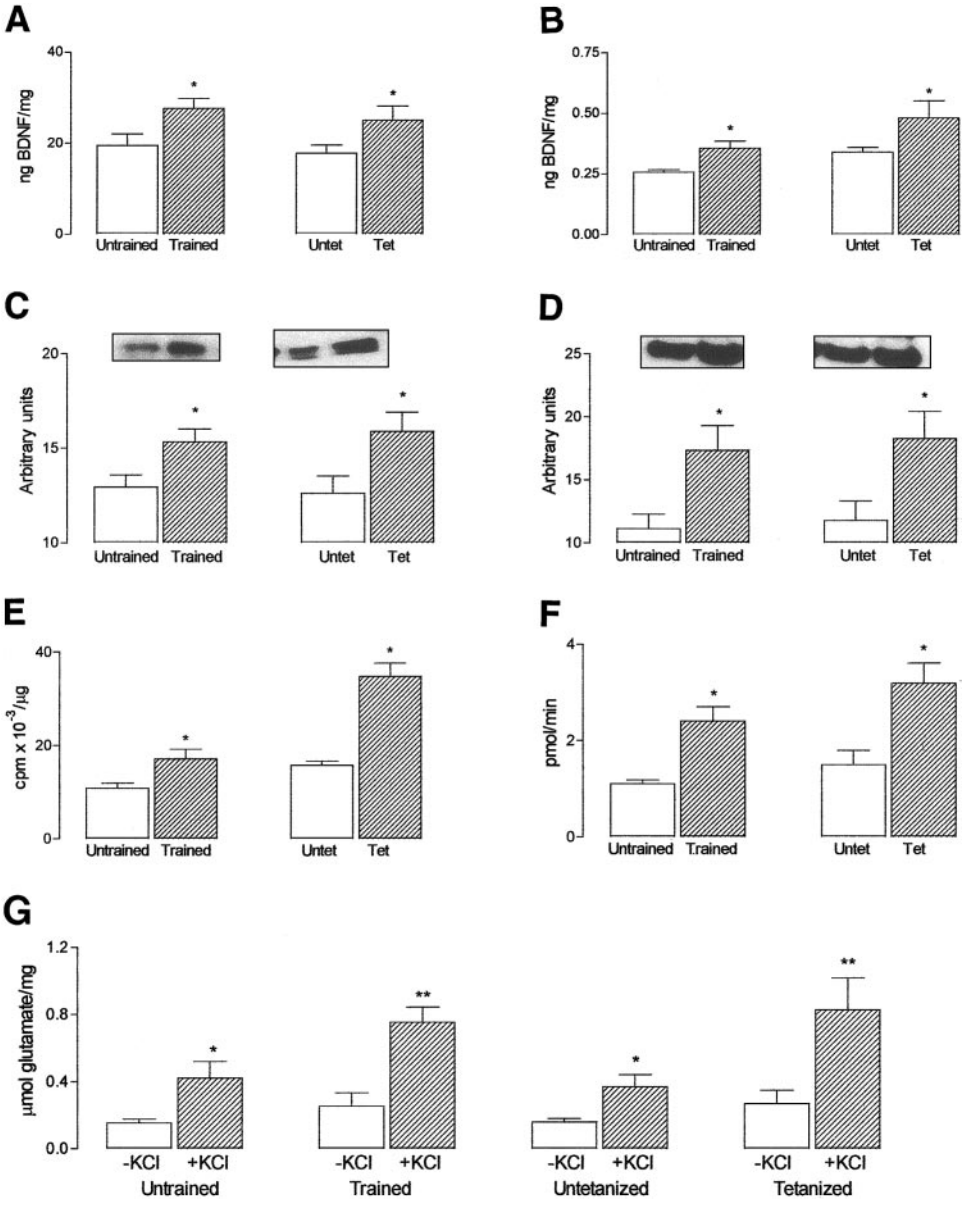

FIG. 4. Brain-derived neurotrophic factor (BDNF) concentration was significantly increased in homogenate prepared from dentate gyrus of rats which underwent training in the Morris water maze (trained) compared with rats which served as yoked controls (untrained); a parallel increase was observed in homogenate of dentate gyrus prepared from rats which sustained LTP in perforant path-granule cell synapses following tetanic stimulation (tetanized; tet) compared with untetanized tissue (untet; $P < 0.05$ in both cases; ANOVA; *A*). KCl-induced BDNF release in slices prepared from dentate gyrus was significantly enhanced in tissue prepared from tetanized, compared with untetanized tissue and in trained, compared with untrained, rats ($P < 0.05$ in both cases; ANOVA; *B*). Phosphorylation of TrkB (*C*) and ERK (*D*) was significantly enhanced in synaptosomes prepared from dentate gyrus of rats which underwent training and those which sustained LTP [$P < 0.05$ in all cases; ANOVA; compare *lane 2* (experimental) with *lane 1* (control) in all sample immunoblots]. Phosphoinositide turnover was significantly enhanced in synaptosomes prepared from dentate gyrus of rats which underwent training and those which sustained LTP ($P < 0.05$ in both cases; ANOVA; *E*). Activity of PKC was significantly enhanced in synaptosomes prepared from dentate gyrus of rats which underwent training and those which sustained LTP ($P < 0.05$ in all cases; ANOVA; *F*). Glutamate release was significantly enhanced by incubation of synaptosomes in KCl (* $P < 0.05$; ANOVA), but a further enhancement was observed in synaptosomes prepared from dentate gyrus of rats which underwent training and those which sustained LTP (** $P < 0.01$ in both cases; ANOVA; *G*).

in hippocampus was not surprising. The evidence suggested that this was a consequence of increased IL-1β concentration, which enhanced activation of superoxide dismutase (SOD), the enzyme which catalyzes the conversion of superoxide to H_2O_2, without affecting the activities of catalase or glutathione peroxidase, the enzymes which catalyze conversion of H_2O_2 to oxygen and water. The data indicated that treatment with antioxidant vitamins E and C overcame the inhibitory effects of stress on LTP and, in parallel, prevented the increased ROS accumulation in hippocampus (629). Consistent with these findings is the observation that LTP in CA1 is impaired in transgenic mice that overexpress SOD (180, 320, 610). It was shown in these studies that LTP could be rescued by treatment with catalase or the antioxidant *N-tert*-butylphenylnitrone (180), diazepam (320) or by inhibition of SOD (610). These effects have been variously interpreted as indicating that the increase in H_2O_2 accumulation resulting from increased SOD activity diminishes LTP (180) and conversely that superoxide is necessary for expression of LTP (610). Predictably, the inhibitory effect of intracerebroventricular injection of H_2O_2 on LTP, at a concentration which increased accumulation of ROS in hippocampus, was overcome by pretreatment with the antioxidant phenylarsine oxide (629).

Parallel assessments on LTP and spatial learning were conducted in some studies. The data obtained from these experiments indicated that the impairment in LTP that was observed in transgenic mice that overexpressed SOD was accompanied by a deficit in spatial learning supporting the view that similar mechanisms underlie the expression of LTP and learning (318, 610).

C. Irradiation Stress

Among the several effects of irradiation is an increase in ROS production (341, 518), and some effects of exposure of cells to ROS are mimicked by exposure of cells to ionizing radiation. In the present context, it is significant that a recent study demonstrated that exposure to whole body irradiation resulted in an increase in ROS accumulation in hippocampus (341). Assessment of LTP in these rats revealed a marked attenuation after irradiation. The first observation of such an effect was reported by Pellmar and colleagues (489, 491, 614) who demonstrated that LTP was markedly reduced in slices of CA1 prepared from guinea pigs that had been exposed to γ-irradiation; the findings from this laboratory indicated that the inhibitory effect of irradiation extends to LTP in perforant path-granule cell synapses in vivo (341). While the effects of irradiation may arise from an accumulation of ROS, the data have indicated that significant cell death occurs in hippocampus of irradiated rats; importantly, it has been shown that the detrimental effects of irradiation on hippocampal function are abrogated by treatment with the polyunsaturated fatty acid eicosapentaneoic acid (341), which has been shown to have anti-inflammatory properties (30, 219).

In parallel with the effect of irradiation on LTP, a number of groups have reported that it also negatively impacts on spatial learning. Deficits in T-maze and water maze performance were observed several weeks after X-ray irradiation; these changes were, to some extent at least, task dependent and dose dependent and were accompanied by evidence of necrosis in the fimbria and degenerative changes in corpus callosum (233). Deficits in spatial learning are not confined to animals that were exposed to X-ray, since exposure to iron-56 particle irradiation has also been shown to impair performance in a spatial learning task (568).

D. Age, LTP, Learning, and Memory

Cognitive deficits in aged rats, particularly deficits in spatial information processing, have been recognized and reported for many years and by several groups (42, 136–138, 405, 509). Correlated with deficits in performance in spatial learning, for example, in the Barnes circular maze, is a deficit in LTP in CA1; thus animals that were relatively unimpaired in spatial learning sustained LTP to some degree, while severely impaired animals did not sustain LTP (31). Interestingly, treatment with the cAMP phosphodiesterase inhibitor rolipram enhanced performance of aged rats, suggesting that a decrease in cAMP and/or cAMP-induced signaling contributes to the age-related change. However, several other changes have been coupled with the age-related decline in spatial memory; for example, mGluR-induced phosphoinositide turnover was decreased with age, and that was linked with decreased PLC-β immunoreactivity (455) whereas the arachidonic acid-induced increase in phosphoinositide turnover in dentate gyrus was decreased in aged rats that exhibited poor spatial learning (358). It was also shown that PKC-γ immunoreactivity in CA1 (but not dentate gyrus) was correlated positively with spatial memory impairment in aged rats (109), while a decrease in PKC activity was shown to accompany the deficit in LTP in aged rats (395). Mitochondrial decay and DNA and RNA oxidation have also been reported to increase with age and to correlate with poor performance in spatial learning (336), and these findings are consistent with the age-related increase in ROS accumulation that we have repeatedly observed, and which is coupled with impaired LTP and with evidence of inflammation (217, 462). Interestingly, chronic treatment of aged rats with aspirin, which combats inflammation, markedly improved performance in a spatial learning task in the aged rats (574). Consistent with the idea that accumulation of ROS impacts on membrane composition by decreasing arachidonic acid concentration is the finding that the decline in spatial learning, like the impairment in LTP, is coupled with decreased arachidonic acid (AA) concentration in hippocampus (358). Yet another factor that correlates with the decline in spatial learning with age is circulating glucocorticoid concentration (67, 442); the coupling between these factors was recently consolidated by the finding that chronic antidepressant treatment abrogated the age-related decline in spatial learning and the attendant increase in glucocorticoids (655).

In the past it was considered that cell loss in the aged brain may be responsible for impairment of spatial learning, but it has been argued that when analysis of neuronal number is undertaken using newer stereological techniques no age-related cell loss is recorded in hippocampus (508) or entorhinal cortex (411). However, in another study it was shown that aged animals that exhibited an impairment in spatial learning had lower hippocampal neuron densities compared with young animals and aged animals that performed well in spatial learning tasks (405). Using a different approach to analysis of cell viability in the aged brain, we observed that the age-related impairment in LTP was associated with evidence of apoptosis in hippocampus; specifically, activation of the so-called cell death enzyme, caspase-3, was enhanced, and TUNEL staining, which identifies nicked DNA, a hallmark of cell death, was increased (380).

There is a general agreement that maintenance of LTP is markedly impaired with age (41, 43, 129, 307, 308, 356, 392, 441, 442), but although some groups have observed an impairment in induction (356, 392, 441), others (e.g., Refs. 41, 146) have not. There is some variability in the extent of the age-related deficit in LTP with profound effects observed in some rats and little impairment in

others (356, 392). One might argue that such variability is to be expected and parallels performance of aged animals in spatial learning tasks (e.g., Refs. 358, 507, 508).

Clearly a major goal in neuroscience is to identify the underlying cause of the age-related deficit in LTP, but this is not trivial given the array of changes that have been documented in the aged brain. Many of these changes may be a consequence of the alterations in membrane characteristics that might be expected to impact on membrane function, and among these is the age-related increase in accumulation of ROS (102, 664; Fig. 4) arising from an increase in SOD activity in the absence of concomitant changes in activities of glutathione peroxidase or catalase (87, 191, 466, 467). Increased ROS accumulation is closely coupled with increased concentration of IL-1β, and these changes have been correlated with deficits in LTP in the aged animal (400, 441, 442, 467, 627, 628). The consequences of a chronic increase in ROS production are profound and lead to lipid peroxidation, which in turn results in a decrease in the membrane concentration of polyunsaturated fatty acids, altering membrane fluidity (353, 355, 441, 443). A change in membrane composition and fluidity is likely to impact on receptor function; one example of receptor dysfunction is the age-related decrease in NMDA receptor binding and the accompanying changes in cell signaling (69, 92, 122, 249, 291, 365, 599). As described above, NMDA receptor activation initiates a cascade of cellular reactions that is thought to lead to maintenance of LTP; key among these changes is increased intracellular calcium concentration. Although there are no data explicitly indicating that calcium influx through the NMDA-coupled calcium channel is altered with age, there is a great deal of evidence indicating that calcium homeostatic mechanisms are disrupted (304, 306), and this has been explained variously by a decrease in calcium channel number and activity (202, 630) or a decrease in calcium transport or uptake across the mitochondrial membrane. Because signaling molecules such as PKC and CaMKII are calcium sensitive or calcium-dependent, it is not surprising that activation of both is decreased with age (434). However, age is also associated with decreased activation of tyrosine kinase (434), ERK (397), and PI 3-kinase (366a), all of which have been linked with expression of LTP (see above).

One consistent change that accompanies LTP in dentate gyrus, although not necessarily other hippocampal areas, is an increase in transmitter release, and data from several experiments have indicated that the age-related decrease in LTP is coupled with a decrease in depolarization-induced glutamate release (356, 392, 397–400). An age-related decline in the expression of synaptophysin, an important synaptic vesicle protein involved in transmitter release, has been reported (435, 538) and may contribute to the decrease in transmitter release. However, evidence suggests that a significant factor may be the increase in IL-1β, which is inversely correlated with glutamate release (283, 443) and LTP (352a, 629) and also with concentration of polyunsaturated fatty acids in hippocampal membrane (353, 355).

Because the more persistent components of LTP rely on protein synthesis and probably morphological changes, it is significant that an age-related decrease in protein synthesis has been reported (197, 284, 435), and this has been identified as a possible factor that contributes to the decrease in neuronal density (405). This decrease in neuronal density (305) is coupled with a decrease in synaptophysin expression (435, 538) and synaptic density (e.g., Refs. 58, 59, 128, 538, 550). In addition, while LTP has been associated with an increase in the number of nonperforated synapses (188), aging is associated with a reduced number of such synapses (187). More recently, it was established that the number of synaptic contacts per neuron is reduced in aged, compared with young, animals (190), while a decrease in synapses with multiple, completely partioned, transmission zones was observed in aged rats that exhibited impaired LTP (189).

Data from several studies have indicated that the impairment in LTP in aged rats is associated with a decrease in membrane polyunsaturated fatty acids, specifically AA and docosahexanoic acid (DHA), and treatment of aged rats with either of these polyunsaturated fatty acids has been shown to reverse the age-related decrease in LTP and the decrease in membrane concentration of the fatty acid (392, 397–400). While restoration of membrane properties is one mechanism by which fatty acids act to reverse age-related impairments, AA and DHA have been shown to modulate hippocampal synaptic plasticity; for example, AA induces potentiation of the synaptic response (460, 643), and both DHA and AA potentiate NMDA-induced responses (457). In support of the idea that these fatty acids may have a specific role in signaling are the observations *1*) that the attenuation of LTP, which is associated with inhibition of phospholipase A_2, is rescued by AA and DHA (174) and *2*) that AA-induced facilitation of the synaptic response in CA1 occluded tetanus-induced LTP (460).

In parallel with the facilitatory effect of DHA on LTP, maze learning has been reported to be enhanced in DHA-treated mice (327, 328) or rats treated with the AA precursor γ-linoleic acid (143). Similarly, chronic treatment with DHA that increased cortical and hippocampal concentration of the fatty acid also improved reference memory in young rats (183). Consistent with this, DHA deficiency has been associated with decreased exploratory behavior, compromises in working memory, spatial learning in the Morris water maze, and also olfactory cued reversal learning (86, 152, 540, 633). Indeed, the impairment in maze learning in aged mice (328), as well as the age-related increase in the number of errors in working and reference memory, as assessed in the radial arm

maze, were associated with decreased DHA (183), and in all cases DHA treatment improved performance. Interestingly, DHA has also been shown to attenuate low-frequency stimulation (LFS) induced LTD in CA1 in vitro (658). The age-related decrease in AA has also been coupled with cognitive deficits (622). Although it is likely that the primary effect of deficiency in polyunsaturated fatty acids is a consequence of its effect on the membrane, it has been reported that NGF is decreased in parallel with DHA deficiency (246); interestingly, decreased NGF concentration has been coupled with deficits in spatial learning and LTP in the aged animal (see above). Thus, in general terms, the parallel impairments in learning and LTP, which are associated with reduced concentrations of DHA, represent a striking parallel between LTP and certain forms of learning/memory.

The impairment in LTP in aged rats that was associated with increased ROS accumulation was also associated with a decrease in vitamin E concentration; both AA and DHA have been shown to have some antioxidant effects (355), and their beneficial effects in aged rats may be partly attributable to this, while the beneficial effects of lipoic acid have also been attributed to its antioxidant properties (354). Thus lipoic acid reversed the age-related increase in ROS accumulation and also reversed the impairment in LTP in aged rats (399). Lipoic acid has also been reported to improve performance of aged mice in an open-field memory test (592, 593), and this effect has been coupled with its ability to alleviate the age-related deficit in NMDA receptor-associated signaling (592, 593). Consistent with the idea that accumulation of ROS may trigger changes leading to the deficit in LTP are the findings that vitamin E deficiency resulted in attenuation of LTP (651), while vitamin E treatment, like fatty acid treatment, reversed the age-related impairment in LTP (441). It was recently reported that dietary manipulation with antioxidants reversed the age-related impairment in spatial learning; this change was coupled with a decrease in ROS accumulation and with enhanced vitamin E concentration in hippocampus (268). Interestingly, vitamin E supplementation in apolipoprotein E-deficient mice for 12 mo also led to a significant improvement in their performance in spatial learning (626).

E. Cognition and Inflammation

Neurochemical parameters involved in learning and memory processes are sensitive to immune-active molecules, and similarly, brain areas, for example, the hippocampus, have also been shown to be sensitive to these same molecules. For example, several reports have indicated that cognitive function is disrupted by neuronal inflammation, for example, following IL-1β or LPS treatment (see above). Significantly, deficits in cognitive function associated with inflammation have also been reported in human subjects receiving cytokine treatment for cancer and hepatitis.

1. IL-1β, LTP, learning, and memory

An increase in hippocampal IL-1β concentration has been consistently shown to inhibit LTP. Thus intracerebroventricular injection of IL-1β inhibited LTP in perforant path-granule cell synapses (283, 353, 441, 442, 467; Fig. 4), and this finding is supported by data from several experiments that were conducted in vitro and that revealed that application of IL-1β to hippocampal slices inhibited LTP in dentate gyrus (118), CA1 (54), and CA3 (279). Consistently, LTP has been shown to be impaired in several circumstances in which IL-1β concentration in hippocampus is increased, for example, in aged (380, 442, 441, 627) and stressed (442, 629) rats, rats treated with LPS (627), and rats exposed to γ-irradiation (A. M. Lynch, M. Moore, S. Craig, P. E. Lonergan, and M. A. Lynch, unpublished data; see Fig. 5). In parallel with the inhibitory effect of IL-1β on LTP is the finding that IL-1β exerts an inhibitory effect on various hippocampal-dependent forms of learning. For instance, contextual fear conditioning is inhibited by IL-1β, while IL-1ra suppresses the inhibitory effect of stressors, for example, social isolation, on this form of conditioning (368, 502–504). Immunodeficiency virus-1 coat protein gp120 also impairs contextual fear conditioning, and its effect is also inhibited by IL-1ra (502). Unlike contextual fear conditioning, auditory-cue fear conditioning is a hippocampal-independent form of learning, and although it is impaired by gp120, this form of learning does appear not to be sensitive to IL-1β (502). Further evidence of a role for IL-1β-induced inhibition in hippocampal-dependent learning paradigms are the findings that it inhibits learning in the Morris water maze (181, 192, 469) and that it mediates the *Legionella pneumophilia*-induced impairment in spatial learning navigational learning (193).

Injection of LPS induces an increase in IL-1β expression in hippocampus (342, 627), and consistent with the findings that increased IL-1β negatively correlates with maintenance of LTP is the observation that LPS inhibits LTP in perforant path-granule cell synapses (462, 627). Like IL-1β, LPS treatment has also been shown to inhibit spatial learning (561), whereas it led to a deficit in contextual, but not auditory-cue, fear conditioning in rats. The LPS-induced effect was inhibited by IL-1ra, indicating that it was mediated by IL-1β (503). Performance in passive avoidance tasks and in the elevated maze is diminished in both aged and LPS-treated mice; chronic administration with nonsteroidal anti-inflammatory agents has been shown to restore function (255), which provides support for the idea that inflammation in brain tissue leads to deficits in learning/memory. Similarly a recent

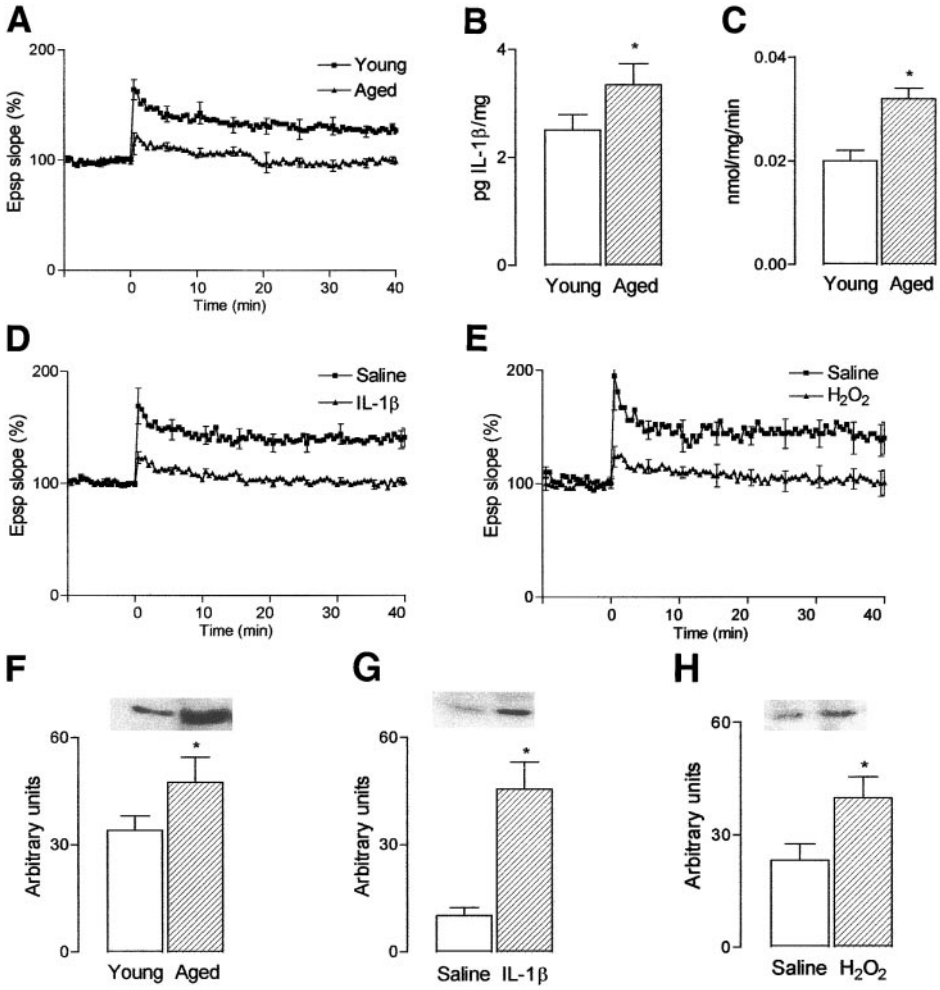

FIG. 5. LTP in perforant path-granule cell synapses was markedly attenuated in urethane-anesthetized aged, compared with young, rats (*A*) and age-related increases in both interleukin (IL)-1β concentration (*B*) and reactive oxygen species accumulation (*C*) were observed in hippocampal homogenate ($P < 0.05$; Student's *t*-test for unpaired samples). LTP was also attenuated in rats treated intracerebroventricularly with IL-1β (*D*) or H_2O_2 (*E*). Activation of JNK was significantly increased in hippocampal tissue prepared from aged, compared with young, rats [*F*; IL-1β-treated compared with saline-treated rats (*G*) and H_2O_2-treated compared with saline-treated rats (*H*); $P < 0.05$; Student's *t*-test for independent samples; compare *lane 2* (experimental) with *lane 1* (control) in the sample immunoblots].

study has shown that the LPS-induced impairment in spatial memory in young rats was suppressed by a novel nonsteroidal anti-inflammatory drug, NO-flurbiprofen, but this was not the case in aged rats (218). Similarly, the LPS-induced impairment in LTP, as well as the associated activation of microglia, was inhibited by treatment with NO-flurbiprofen (217).

2. *What signaling cascades are activated by IL-1β and ROS in hippocampus?*

If IL-1β and/or ROS are responsible for the impairment in LTP associated with age and various stresses, then it is appropriate to consider the downstream consequences of increases in IL-1β concentration and ROS accumulation in hippocampus. Among the changes that have been consistently observed is an increase in activation of the mitogen-activated protein kinases, c-jun NH_2-terminal kinase (JNK) or stress-activated protein kinase (SAPK), and p38 in hippocampus of LPS- and IL-1β-treated rats (627, 628) and aged rats (380, 467); indeed, the age- and IL-1β-induced increases in JNK activation are paralleled by an increase in JNK activation due to H_2O_2 injection (Figs. 5 and 6). Recent studies have indicated that similar increases in activation of these kinases occur in hippocampus of rats exposed to whole body irradiation (341). In all cases, LTP was impaired, and the evidence indicated that there was a negative correlation between JNK and p38 activity and LTP. Recent evidence has indicated that IL-1-associated signaling cascades are upregulated with age; thus increased expression of IL-1 type I receptor (IL-1R1) and activation of IL-1 receptor-associated kinase (IRAK) may contribute to the increased transduction of the IL-1β signal leading to enhanced activation of p38 and JNK (352a). Significantly, we have recently found evidence of age-related cell death in hippocampus (352a) and entorhinal cortex (380), and the findings suggest that activation of stress-activated kinases plays a key role in triggering these changes. It is significant that the IL-1β-induced impairment in LTP was coupled with increased activation of p38 and JNK and that treatment with vitamins E and C reversed both the impairment in LTP and the enhancement in activity of the kinases (629). We

have found that IL-1β inhibits glutamate release in vitro and that release in hippocampal tissue prepared from IL-1β-treated rats is also decreased; recent evidence suggests that the effect of IL-1β is mediated through activation of p38 and JNK, since inhibitors of these kinases abrogate the IL-1β-induced attenuation of release. In parallel, we have found that the inhibitory effect of IL-1β on release and LTP is suppressed by pretreating IL-1β-injected rats with SB203580 (285a). Interestingly, the age-related impairment of LTP and the accompanying increases in IL-1β concentration and JNK and p38 activation are all reversed by treatment of rats with the *n*-3 polyunsaturated fatty acid DHA (628) and its precursor, eicosapentaneoic acid (380).

3. LTP, cognitive function, and β-amyloid

Several hallmarks of oxidative stress and inflammation have been shown to be present in Alzheimer's disease (AD; Refs. 377, 576). Because of this, it has been suggested that chronic treatment with LPS results in changes that mirror those of AD, and therefore, it has been useful as a model of the disease. Among the effects of LPS infusion are activation of astrocytes and microglia particularly in hippocampus and temporal lobe, increased proinflammatory cytokines like IL-1β and tumor necrosis factor-α, increased amyloid precursor protein (APP) mRNA, and evidence of neuronal degeneration (216). Evidence of oxidative stress has also been identified in transgenic mouse models of AD (575), and this is accompanied by an increase in IL-1β concentration and β-amyloid deposition, both of which are attenuated by ibuprofen treatment (326). In these models, such changes have been coupled with impairments in spatial learning (626), and one model, which overexpresses human APP with age, is associated with amyloid deposits and high concentrations of the mutant β-amyloid. These animals exhibit memory deficits and deficits in LTP (97); indeed, the appearance of β-amyloid aggregates coincided with the first evidence of memory impairment (640). Similarly it has been shown that intrahippocampal injection of β-amyloid led to aggregation of amyloid material and evidence of inflammation several weeks after treatment, and at this time, there was evidence of deficits in LTP and in working memory (589).

4. Gene expression and age

In contrast to the profound age-related changes in several signaling pathways that are triggered by LTP (or LTP stimulating protocols) in hippocampus, analysis of several IEGs in tissue prepared from young and aged rats revealed a surprising lack of change; indeed, the only significant change was an age-related increase in c-*fos* expression. In a parallel study in which expression of c-*fos* and tissue plasminogen factor was assessed after seizure activity, both IEGs were apparent in aged and young rats, but the level of change and the response time were compromised; in contrast, seizure-induced expression of microtubular-associated protein 1B was more rapid and enhanced with age (553). However, in a recent DNA microarray analysis of the aged brain, Prolla and colleagues (316, 500) reported induction of certain IEGs, specifically junB and c-*fos*. In addition, there was a marked upregulation of several genes that are associated with immune or inflammatory responses, including induction of several components of the complement cascade, while upregulation of genes associated with the stress response, for example, several heat shock proteins, was observed. These findings are consistent with several reports of inflammatory and stress-associated changes in the aged brain.

VIII. LONG-TERM POTENTIATION AND MEMORY: DO THEY SHARE CELLULAR MECHANISMS?

If it is argued that the same set of synapses are activated and modified in the same way by LTP and spatial learning, then it follows that saturation of LTP would impair learning (and vice versa). Several groups have addressed this question by parallel analysis of spatial learning and LTP. Some of these studies showed that saturating LTP impaired spatial learning in two separate learning tasks (94, 407, 429). These authors concluded that both processes, LTP and spatial learning, relied on the same cellular mechanisms, and the data were considered to provide strong support for the proposal that LTP was a model for at least some forms of learning. However, others (see Ref. 65) have failed to substantiate this finding, although there was some indication in one study that rats previously trained in the water maze exhibited a small reduction in ability to sustain LTP (259). As pointed out (see Refs. 65, 258), there are several reasons why saturating LTP might not block learning; LTP may have been induced in the wrong pathway, in too few fibers, or to a lesser extent than is required to block subsequent learning. Indeed, it is known that stimulation at a single site does not saturate LTP in all perforant path-granule cell synapses (44), and it has also been suggested that LTP saturation would need to be complete to block learning since learning requires synaptic modification in a relatively small fraction of hippocampal tissue (428). Data from a recent study have added a new dimension to these deliberations; it was shown that LTP in CA1 of conscious rats was persistently reversed when these rats were allowed to explore a novel (nonstressful) environment; the authors reported that theta activity was enhanced during reversal and proposed that this may induce depotentiation in the recently potentiated synapses (653). These

findings indicate that data obtained from the "classical" saturation experiments may be confounded by coexistence of potentiation and depotentiation of synaptic responses at specific synapses in a given area.

In addition to these data, it is appropriate to reflect on some of the evidence which indicates that similar cellular/molecular mechanisms are responsible for spatial learning (specifically performance in the Morris water maze) and for maintenance of LTP. For example, both are associated with certain biochemical changes such as increased glutamate release, inositol phospholipid turnover (393), and activation of several kinases, for example, PKC and ERK (Fig. 6). Activation of IEGs and transcription factors, increased protein synthesis, alterations in neurotrophin expression, and alterations in calcium handling by cells have also been reported. In addition, both LTP and spatial learning induce increases in BDNF concentration in dentate gyrus, increased KCl-stimulated release of BDNF, and increased TrkB phosphorylation (199; Fig. 6) which may contribute to the observed changes in ERK activation. Further indirect support for the view that LTP may be a biological substrate for some forms of learning is the significant body of evidence which indicates that both spatial learning and LTP are compromised in stressed rats and aged rats (see above). However, one of the most frequently quoted examples is that both are inhibited by AP5 (425), and recent work has elaborated on this finding. It was shown that AP5 only impairs spatial learning in task-naive animals, while subjects pretrained in a spatial task are resistant to the effect of AP5 (430, 478). NMDA antagonists, AP5 and NPC17742, blocked LTP but failed to block spatial learning in pretrained rats, suggesting that the relationship between LTP and spatial learning is not direct and raising questions relating to the precise role of NMDA receptor activation in spatial learning.

Is it reasonable to suggest that LTP is a model for learning and/or memory? There is no doubt that consolidation of memory requires some form of synaptic remodeling, and this fundamental requirement is at the heart of the idea that LTP, which also relies on synaptic remodeling, might replicate the cellular changes that occur during memory formation. This idea is supported by a great deal of circumstantial evidence. First-order support includes the fact that LTP is robustly supported by the major afferent pathways in the hippocampus, an area of the brain with a profoundly important role to play in memory formation, and that certain properties of LTP (cooperativity, associativity, and specificity) are precisely the properties that might be anticipated as important in consolidation of memory. Second-order support is provided by an enormous body of data which suggests that certain forms of memory invoke stimulation of synaptic events that play a role in the establishment of LTP, and this includes evidence that certain forms of memory are inhibited by agents that also inhibit LTP. However, it has to be considered that even when the conscious animal is used in the analysis of LTP (and therefore multiple inputs may be activated), recordings are made from specific populations of cells in response to a specific input from a specific collection of fibers. In contrast to this relatively well-controlled situation, consolidation of memory during

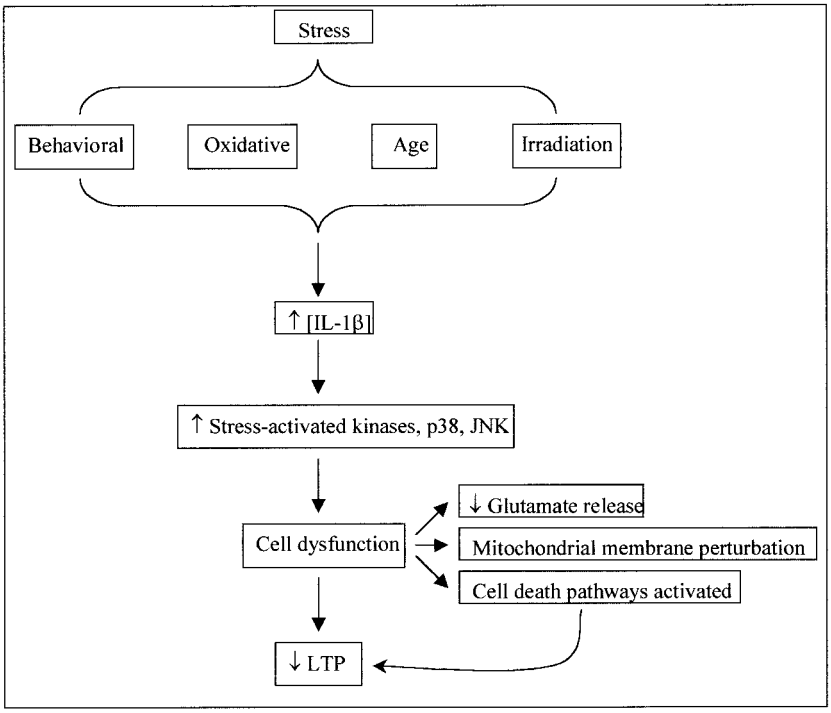

FIG. 6. Stressors (e.g., behavioral, oxidative, and irradiation as well as age) all lead to increased IL-1β concentration in brain, specifically hippocampus, which in turns stimulates stress-activated protein kinases, JNK and p38. Evidence indicates that these changes result in cell dysfunction and consequently impacting on synaptic function.

TABLE 5. *Transgenic mice, LTP, and spatial learning/memory*

	Mutant	LTP	Spatial Learning/Memory	Reference No.
Glutamate receptors	NMDA-R in CA1 absent	LTP in CA1 impaired	Impaired spatial learning	617, 618
	NMDAε1 subunit knockout	LTP in DG impaired	No details	385, 539
	Point mutation in glycine binding site of NMDA-R		Impaired spatial learning	287
	Overexpression of NR2B	LTP in CA1 enhanced	Enhanced spatial learning	605
	Overexpression of NR2D	LTP in CA1 impaired	Spatial learning normal	470
	mGluR5 knockout	LTP in CA1, DG impaired	Impaired spatial learning	263, 348
	mGluR2 knockout	LTP in CA1 enhanced	Reduced exploration: therefore effect on spatial learning/memory undetermined	263, 348
	GluR6 knockout	LTP in DG unaffected LTP in mf-CA3 impaired	Spatial learning normal	112, 632
Other receptors	5-HT (1A) receptor knockout	LTP in CA1 unaffected	Impaired spatial learning	543
	5-HT-3C receptor knockout	LTP in DG impaired	Impaired spatial learning	223
	PAF receptor knockout	LTP in DG impaired	No details	98
	TNF receptor knockout	LTP in CA1 unaffected	No details	15
	Nociceptin knockout	LTP in CA1 enhanced	Enhanced spatial learning	461
	Mu-opioid receptor knockout	LTP in DG impaired LTP in CA1 unaffected	No details	386
	Muscarinic (M1) receptor knockout	LTP in CA1 impaired	Nonmatching to sample working memory impaired	22
	TrkB knockout	LTP in CA1 impaired	Impaired spatial learning	419
Signaling	Expression of inhibitory PKA regulatory subunit, i.e., R(AB) mice	LTP in CA1 impaired	Impaired spatial learning	3, 650
	Cβ1 and R1β PKA mutants	LTP in mf-CA3 impaired LTP in CA1 unaffected	Spatial learning unaffected	237
	AC1 + AC8 knockout	LTP in CA1 impaired	Impaired spatial memory	649
	αCaMKII knockout	LTP in CA1 impaired	Impaired spatial memory	194, 230, 570, 572
	Dendritic αCaMKII "knockout"	LTP in CA1 impaired	Impaired spatial memory	418
	Expression of calcium-independent CaMKII	LTP in CA1 impaired	Impaired spatial memory	388
	Expression of CaMKII-Asp-286	LTP in CA1 impaired	Impaired spatial memory	32
	Expression of inhibited αCaMKII	LTP in CA1 impaired	Impaired spatial learning	150
	CaMKIV/Gr knockout	LTP in CA1 impaired	Spatial learning unaffected	232
	Expression of dominant negative CaMKIV	LTP in CA1 impaired	Impaired spatial learning	274
	PKC-γ knockout	LTP in CA1 impaired	Impaired spatial learning	4, 5
	ERK1 knockout	LTP in CA1 unaffected	Spatial learning unaffected	559
	Targeted disruption of α and δ CREB	LTP in CA1 impaired	Impaired spatial learning	74
	Fyn knockout	LTP in CA1 impaired	Impaired spatial learning	205, 295
	c-*kit* receptor tyrosine kinase knockout	LTP in mf-CA3 reduced LTP in CA1 unaffected	Impaired spatial learning	276
	EphB2 knockout	LTP in CA1 and DG impaired		224
	SynGAP knockout	LTP in CA1 impaired	Impaired spatial learning	297
	PTPδ knockout	LTP in CA1 and CA3 impaired	Impaired spatial learning	621
	Targeted disruption of Zif268	LTP in DG impaired	Impaired spatial memory	267
	IP_3R1 knockout	LTP in CA1 enhanced	No details	173
	IP_3 3-kinase knockout	LTP in CA1 enhanced; LTP in DG unaffected	Spatial learning unaffected	271
	RyR3 knockout	LTP in CA1 enhanced	Enhanced spatial learning	178
	RyR3 knockout	LTP in DG and CA1 unaffected	Impaired spatial learning	38
	ApoE knockout	LTP in CA1 impaired	No details	468, 624
Presynaptic proteins	Complexin II knockout	LTP in CA1 impaired	No details	602
	Synaptophysin + synaptogyrin knockout	LTP in CA1 impaired	No details	256
	Overexpression of GAP43	LTP in DG enhanced	Enhanced spatial learning	532
	Rab3A (RIM1α subunit) knockout	LTP in mf-CA3 impaired	No details	91
	Synapsin knockout	LTP in CA1 and CA3 unaffected	No details	580

TABLE 5—*Continued*

	Mutant	LTP	Spatial Learning/Memory	Reference No.
Structural proteins	NCAM L1 knockout	LTP in CA1 unaffected	Impaired spatial learning	63, 165
	NCAM knockout	LTP in CA1 impaired		437
	Telencephalon-specific cell adhesion molecule knockout	LTP in CA1 enhanced	Enhanced spatial learning	448
	Integrin-associated protein knockout	LTP in DG impaired	Impaired memory retention	96
	Tenascin-R knockout	LTP in CA1 impaired	Spatial learning unaffected	154, 537
	Thy-1 knockout	LTP in CA1 unaffected LTP in DG impaired	Spatial learning unaffected	463
	Brevican knockout	LTP in CA1 enhanced	Learning/memory unaffected	77
	LIM kinase 1 knockout	LTP in CA1 enhanced	Impaired spatial learning	410
Other proteins	Galanin knockout	LTP unaffected	Deficit in object recognition memory	383
	Overexpression of galanin	LTP in DG impaired	Impaired spatial learning	115
	Neuropsin knockout	LTP unaffected	Spatial learning unaffected	119
	Calbindin D-deficient mice	LTP in CA1 impaired		269, 422
	Neurogranin knockout	LTP in CA1 impaired	Impaired spatial learning	482
	Somatostatin knockout	LTP unaffected	Enhanced spatial learning	148
	Acid-activated ion channel knockout	LTP in CA1 impaired	Impaired spatial learning	639
	S100B knockout	LTP in CA1 enhanced	Enhanced spatial memory	459
	GLT-1 knockout	LTP in CA1 impaired		277
	Overexpression of EC-SOD	LTP in CA1 impaired LTP in CA3 unaffected	Impaired fear conditioning	180, 610
	eNOS knockout	LTP in CA1 impaired	Enhanced spatial learning	169, 646
	Protein phosphatase inhibitor-1 knockout	LTP in CA1 unaffected LTP in DG impaired	Spatial memory unaffected	18
	t-PA knockout	LTP in CA1 impaired	Impaired spatial memory	21, 81
	Overexpression of t-PA	LTP in CA1 enhanced	Enhanced spatial learning	364

training involves activation of numerous modalities which are likely to translate into potentially confounding activation of several pathways and brain areas. Similarly, it is widely acknowledged that there are multiple forms of memory, and there are multiple facets of memory even when consideration is limited to a particular form of memory, for example, spatial memory. Consequently, it has to be acknowledged that reduction of such a complex modality to the form of plasticity that is LTP is simplistic. The converse of this is that there are multiple forms of LTP induced by different paradigms in different synaptic connections and under different experimental conditions, and consequently, it is questionable whether LTP can be considered as a unified construct, without specifying precise experimental conditions.

Despite these drawbacks, it is likely that studies which assess hippocampal LTP and spatial memory will continue to provide valuable evidence in pursuit of the answer to the ultimate question. For instance, it may be valuable to exploit the fact that aged rats fall into categories that range from profoundly impaired in spatial learning (and also LTP, at least in dentate gyrus) to those that are comparable to young rats in terms of performance in spatial learning tasks and in terms of sustaining LTP, to ask additional questions. Similarly, further development in design of arrays of electrodes to allow chronic implantation in several synaptic connections in series, while assessing performance in particular tasks are likely to provide further insight. In the past decade or so, widening the question to consider the relationship between LTP and forms of learning other than spatial has led to significant developments specifically in terms of fear conditioning; it is likely that exploitation of this approach will provide further clarification of the fundamental issues.

Since the early 1980s, a major focus of several groups has been to identify the cell signaling cascades that might underpin consolidation of memory and/or expression of LTP, and consequently, there has been a mushrooming of data implicating a huge array of signaling pathways in either or both. Sifting through the data, one must conclude that a consensus has emerged indicating that both are calcium dependent, CaMKII dependent, and protein synthesis dependent, and in the past few years, some inspirational studies from Malinow's group (323, 564, 565) have identified one particularly significant consequence of the increase in intracellular calcium and activation of CaMKII, i.e., recycling of AMPA receptors. The results of these elegant studies not only have implications for synaptic plasticity but identify a fundamentally important process in neurobiology. Analysis of the signaling pathways that accompany LTP and learning and/or memory has also benefited from the application of advances in biogenetics to neurobiology. Indeed, the question of parallels between LTP and spatial learning has come into

sharp focus with these important developments. Thus, in addition to identifying a role for certain signaling molecules, the study of transgenic animals has provided evidence indicating that the mechanisms that underpin LTP are also important in supporting synaptic modifications that underlie spatial learning. Table 5 lists the findings of several studies in which transgenic animals were assessed, and in many cases, the evidence indicates that both LTP and spatial learning are disrupted in certain transgenic animals including knockout mice, for example, fyn, CaMKII, CREB, PKC, and some glutamate receptor subtypes. Similarly, certain experimental models exhibited neither impairment in spatial learning nor LTP in CA1, for instance, thy-1 knockout (463) and mGluR5 (348) knockout mice. In some cases, LTP was disrupted in one hippocampal pathway but not another, for instance, in dentate gyrus, but not CA1 in thy-1 knockout mice; this lack of concordance between disruption of spatial learning and LTP in CA1 has been interpreted as an indication that a close coupling between LTP and spatial learning may exist in some, but not all, synaptic connections. It has to be concluded also that, although exploitation of genetic techniques provides a very powerful tool, using similar genetic manipulations may yield results that are not entirely reproducible from laboratory to laboratory (see Table 5 for some examples). These apparently inconsistent findings illustrate several of the difficulties in the literature and highlight certain cautionary points. First, it is clear that LTP may be sustained in one synaptic pathway and not in another, bringing into sharp focus the problem that arises when data from one area are used to extrapolate to another. Second, it suggests that different synaptic connections may utilize different signaling molecules. Third, it emphasizes the fact that LTP may be sustained under one set of experimental conditions (e.g., in vitro or in vivo, in the awake animal or in the anesthetized animal), but extrapolation to other experimental conditions may be inappropriate. Finally, identifying the precise behavioral measure and the specific form of LTP (E-LTP or L-LTP) is imperative and may be of importance in reconciling apparently conflicting findings. The critical question is whether LTP represents a biological substrate for learning and/or memory, and the challenge is to design an experiment that can specifically address this question.

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