Molecular Neurobiology

ISSN0893-7648/05/32(3): 223–235/$30.00

Do Stress and Long-Term Potentiation Share the Same Molecular Mechanisms?

Chiung-Chun Huang,[1] Chih-Hao Yang,[1,2] and Kuei-Sen Hsu[1,2,*]

[1]Department of Pharmacology and [2]Institute of Basic Medical Science, College of Medicine, National Cheng Kung University, Tainan City 701, Taiwan

Abstract

Stress is a biological, significant factor shown to influence hippocampal synaptic plasticity and cognitive functions. Although numerous studies have reported that stress produces a suppression in long-term potentiation (LTP; a putative synaptic mechanism underlying learning and memory), little is known about the mechanism by which this occurs. Because the effects of stress on LTP and its converse process, long-term depression (LTD), parallel the changes in synaptic plasticity that occur following the establishment of LTP with tetanic stimulation (i.e., occluding LTP and enhancing LTD induction), it has been proposed that stress affects subsequent hippocampal plasticity by sharing the same molecular machinery required to support LTP. This article summarizes recent findings from ours and other laboratories to assess this view and discusses relevant hypotheses in the study of stress-related modifications of synaptic plasticity.

Index Entries: Stress; long-term potentiation (LTP); *N*-methyl-D-aspartate (NMDA) receptors; extracellular signal-related kinase (ERK); mitogen-activated protein kinase (MAPK); glucocorticoid receptor; hippocampus.

Introduction

Stress is generally defined as any condition that seriously disturbs the physiological and psychological homeostasis of an organism. Cognitive functioning is particularly and dramatically modified by stress *(1)*. Although the acute response to stress is an adaptive mechanism, excessive stress can have severe repercussions, ranging from impairments in learning and memory to enhanced susceptibility of neurons to atrophy or necrosis in response to metabolic challenges *(1–3)*. As part of a system for the formation of stable declarative, contextual, and spatial memory *(4–6)*, the hippocampus is one of the medial temporal lobe structures that are vulnerable to stressful experiences. Depending on the severity and context, stress has been shown to facilitate or impair hippocampal-dependent forms of learning and memory in

Received April 20, 2005; Accepted May 16, 2005.
*Author to whom correspondence and reprint requests should be addressed. E-mail: richard@mail.ncku.edu.tw

Table 1
Three Hypotheses to Explain the Effects of Stress on Hippocampal Synaptic Plasticity

Hypothesis	Summary	References
LTP-like	Stress affects subsequent hippocampal synaptic plasticity, perhaps by sharing common mechanisms required to support LTP.	*9,14,16,27,28*
Metaplasticity	Stress affects subsequent hippocampal synaptic plasticity by exerting a metaplastic effect through the modulation of Ca^{2+} levels.	*2,49,53,61*
Energetic crisis	Stress affects subsequent hippocampal synaptic plasticity through disrupting neuronal energetics.	*2,59,60*

both humans and animals *(3)*. Consistent with these behavioral observations, both in vitro and in vivo electrophysiological studies have indicated that stress impairs hippocampal long-term potentiation (LTP; refs. *7–13*), a putative cellular mechanism underlying learning and memory. Conversely, low-frequency, stimulation-induced long-term depression (LTD) is promoted by such stress *(12–15)*.

If the notion that changes in synaptic efficacy are essential for learning and memory processes is correct, then it is possible that LTP impairment associated with stress may be one neural basis for stress-mediated memory storage deficit. However, the molecular and cellular mechanisms underlying the alteration of the inducibility of LTP and LTD by stress remain unclear. During the recent years, three major hypotheses have been proposed to explain the stress effects on hippocampal synaptic plasticity (Table 1). Because the effects of stress on subsequent LTP and LTD induction are very similar to the changes in synaptic plasticity that occur following the establishment of LTP with tetanic stimulation *(12)*, it has been hypothesized that stress may affect hippocampal synaptic plasticity by sharing common molecular mechanisms required to support LTP *(2,3,16)*—that is, stress produces LTP or LTP-like changes, thereby occluding subsequent LTP induction. The objective of this article is to critically assess the recent correlative observations supporting this opinion and to discuss relevant hypotheses in the study of metaplastic effects or energetic crisis effects of stress on hippocampal synaptic plasticity, thereby allowing progress in understanding the learning and memory impairments associated with stress. Readers are referred to a number of recent comprehensive reviews for more complete discussion on this topic *(2,3,16)*.

Modulation of Hippocampal LTP and LTD by Stress

The first demonstration of a stress-induced modulation of LTP induction was reported in 1987 by Thompson and colleagues *(7)*. They reported that hippocampal slices prepared from adult rats that had experienced unpredictable and inescapable restraint–tailshock exhibited marked impairment of LTP in the CA1 region. This observation suggests that stress can significantly modulate neuronal plasticity in the rodent hippocampus.

Soon after, the same group of researchers extended these results in second study *(8)*, in which they demonstrated that it is the uncontrollable psychological aspect of the shock, rather than a consequence of the shock itself, that exerts the primarily inhibitory effect on the LTP induction. Subsequent studies have shown that stress-induced impairment of LTP lasts for at least 48 h in rats *(10)* and 24 h in mice *(17)* and that stress also blocks LTP induction in the dentate gyrus *(9)*, but not CA3 region, of hippocampus *(18)*. Additionally, other ethologically relevant stressors (such as forced exposure to a brightly lit chamber) have been shown to impair LTP *(13)* and primed

burst potentiation (PBP; a low-threshold form of LTP *[11,19]*) in awake and freely behaving rats. Interestingly, recent work has shown that stress produced by an instinctual fear of a predator blocked PBP but did not block LTP *(20)*, suggesting that PBP could be a more sensitive diagnostic of how behaviorally relevant variables affect hippocampal processing *(3)*. However, the effects of stress on hippocampal synaptic plasticity are not restricted to LTP and PBP. It has been shown that behavioral stress facilitates the induction of LTD in the CA1 region of hippocampus. For example, restraint–tailshock and exposure to a brightly lit chamber facilitate LTD induction both in vitro *(12,14,15)* and in vivo *(13)*. Because the effects of stress on LTP and LTD have been studied much more extensively than PBP, this article focuses on these two forms of hippocampal synaptic plasticity.

Studies have revealed several common features of stress-induced impairment of LTP. First, administration of the glucocorticoid receptor antagonist RU38486 prevented the effects of stress on LTP and LTD in the CA1 region of the hippocampus, both in vivo *(21)* and in vitro *(14,15)*, and administration of specific glucocorticoid receptor agonist RU28362 mimicked the effects of stress to produce a marked decrement in the induction of LTP in the hippocampal dentate gryus, which was blocked by a prior injection of RU38486 *(22)*. Conversely, administration of the mineralocorticoid receptor agonist aldosterone produced a marked enhancement of LTP. These results suggest a specific role of glucocorticoid receptor activation in mediating the inhibitory effect of stress on the hippocampal LTP.

Second, the effects of stress on hippocampal synaptic plasticity in awake, freely moving rats were found to be short-lasting. Acclimatization to, or removal from, the aversive conditions can lead to a rapid loss of the ability to facilitate LTD and to recover the ability to induce LTP, whereas the effects of stress can be prolonged by inducing anesthesia immediately after the stress *(13,23)*. The rapid loss of the ability of stress to affect synaptic plasticity in awake animals after removal from a stressor has been suggested to result from an active process, presumably dependent on the animals being aware of their escape from the aversive environment.

Third, the effects of inescapable behavioral stress (placement on an elevated platform for 30 min) on LTP and LTD induction in the hippocampal CA1 region of anesthetized rats were prevented by the administration of the protein synthesis inhibitor emetine after the stressful experience, suggesting that new protein synthesis is required for stress to affect the induction of both LTP and LTD *(21)*. Consistent with a role for RNA synthesis in mediating the facilitation of LTD by stress, administration of the transcriptional inhibitor actinomycin D prevented the induction of LTD in stressed animals. However, actinomycin D did not significantly affect the blockade of LTP induction by stress. Therefore, it seems likely that stress affects subsequent LTP and LTD induction via different molecular mechanisms.

Fourth, activation of *N*-methyl-D-aspartate (NMDA) receptor subtype of glutamate receptor is required for the stress-induced modification of hippocampal synaptic plasticity. This is based on the observation that the effects of stress on subsequent LTP and LTD induction can be prevented when the animals are given NMDA receptor antagonist before experiencing stress *(12)*, suggesting that Ca^{2+}-dependent changes may be involved. This finding is analogous to the observation that NMDA receptor antagonists prevented the inhibition of LTP induction caused by low-frequency stimulation before LTP-inducing tetanic stimulation *(24)*.

Finally, amygdale (via its projection to the hippocampus) is also critical in mediating the stress-induced impairment of hippocampal LTP. For example, Kim et al. *(25)* found that electrolytic lesions of the amygdale effectively prevented the effect of uncontrollable restraint–tailshock stress on the induction of hippocampal CA1 LTP. Further work from the same laboratory *(26)* has shown that the amygdale neuronal activity during—but not shortly after—stress is essential for the emergence of stress-induced impairment of LTP. These common features of stress effects on

hippocampal synaptic plasticity were found in male adult animals.

Do Stress and LTP Share Molecular Mechanisms?

This section reviews experimental evidence and questions regarding the hypothesis that stress may affect subsequent hippocampal synaptic plasticity by sharing common mechanisms required to support LTP. Although enormous effort by many laboratories has been devoted to this issue, questions remain and the theory has not been universally accepted. The idea that stress and LTP share common molecular mechanisms was originally proposed by Diamond et al. (*27*) and was extended by Shors and Thompson *(28)* and Shors and Dryver *(9)*. A simple logic is that if stress shares common mechanisms with LTP in vivo, then there should be a saturated LTP of synaptic transmission observed following stress. However, it remains a challenging task to demonstrate that acute or chronic stress produces saturated LTP.

To date, there has been only one report showing that acute stress induced by contextual fear conditioning causes an increase in synaptic excitability up to the 7-d delay, as shown by input–output curve changes *(29)*. The findings of that study indicate that a fear-provoking experience can produce a durable, LTP-like increase in excitability intrinsic to the hippocampus. However, Xu et al. *(13)* found that exposure to a novel stressful environment enabled LTD and blocked LTP but did not induce LTP of synaptic transmission in the hippocampal CA1 region in vivo.

In an attempt to make sense of this confusing literature, we recently re-investigated the effects of acute restraint–tailshock stress on the properties of basal synaptic transmission in the CA1 region of the hippocampus. To determine whether the basal synaptic transmission at the Schaffer collater-CA1 synapses was altered by stress, we compared stimulus–response relationships for extracellular field postsynaptic potential (fEPSP) obtained from control and stressed rat slices. Analysis of evoked fEPSPs revealed no differences in stimulus–response curves, maximal response, and fEPSP waveform in slices from stressed and control rats (Fig. 1A). To examine the effects of stress on NMDA receptor function, NMDA-receptor-mediated fEPSPs were isolated with the use of a solution containing bicuculline methchloride (20 μ*M*), cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 μ*M*), and 0.5 m*M* of Mg^{2+}.

As shown in Fig. 1B, stimulus–response curves of $fEPSP_{NMDA}$ were similar in slices from control and stressed rats. Similarly, the contribution of NMDA receptors to evoked excitatory postsynaptic current (EPSC) by measuring the NMDA receptor currents ($EPSC_{NMDA}$) relative to the size of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor currents ($EPSC_{AMPA}$) recorded at holding potential of –80 and +40 mV was unaltered in CA1 pyramidal cells in slices from stressed rats (Fig. 1C). These results suggest that the basal synaptic transmission and function of NMDA receptors remain normal following stress.

It is well-known that LTP can be reversed by various manipulations when administrated within a time-window of induction *(30,31)*. This reversal of synaptic strength from the potentiated state to pre-LTP levels has been called "depotentiation" and may provide a mechanism for preventing the saturation of synaptic potentiation and increase the efficiency and the capacity of information storage of neuronal networks. If LTP or LTP-like changes occur in the hippocampus during behavioral stress (thereby occluding the subsequent LTP induction), depotentiation treatment should restore the ability of stressed neuronal networks to induce LTP. More recently, we provided convincing evidence that hippocampal CA1 LTP can be normally elicited by high-frequency tetanic stimulation in slices from stressed rats that have previously received depotentiating stimulation (Fig. 2; ref. *14*). These findings favor the assumption that stress may impair subsequent LTP by sharing common molecular mechanisms required to support LTP.

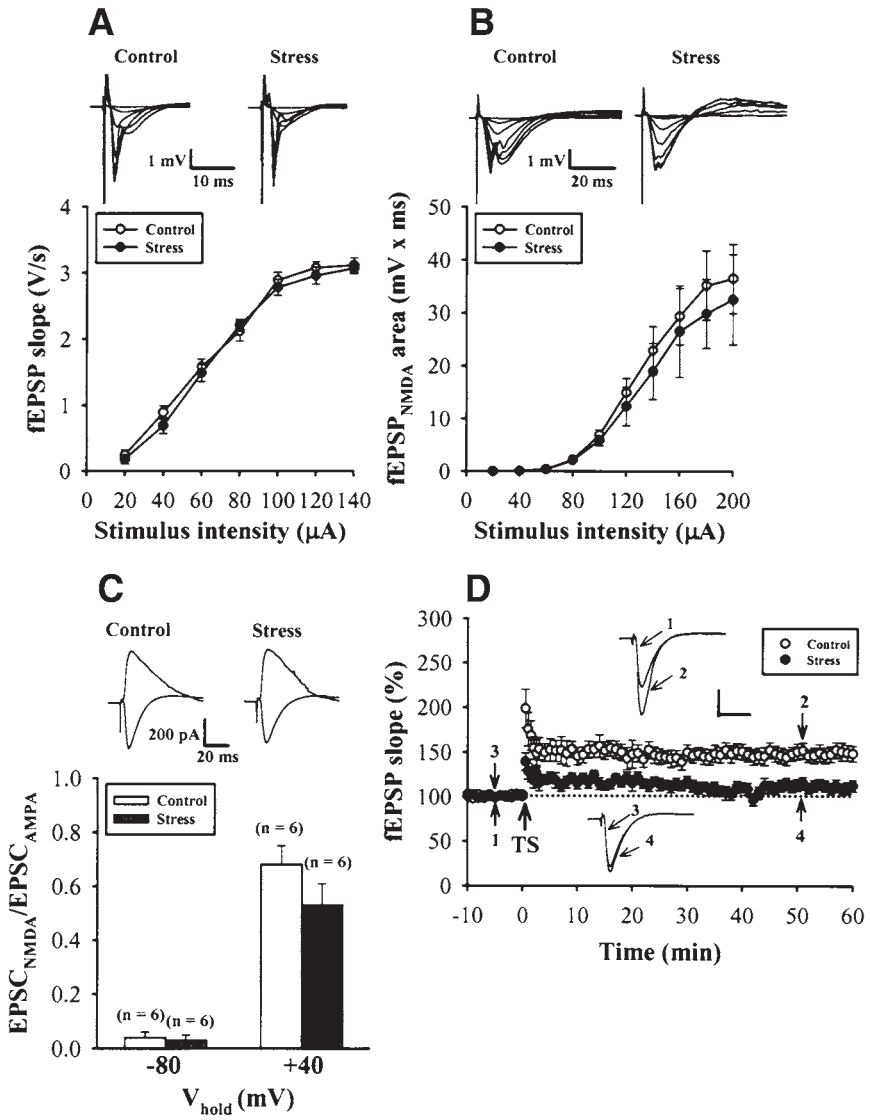

Fig. 1. Basal properties of synaptic transmission at Schafferare/collateral-CA1 synapses are unaltered by restraint–tailshock stress. Behavioral stress was evoked by 60 tailshocks (1 mA for 1 s, 30–90 s apart) as rats were restrained in a Plexiglas tube. Promptly after stress, rats were killed and hippocampal slices (400-μm thick) were prepared for electrophysiological recordings. **(A)** Input–output curve of fEPSP (V/s) vs stimulus intensity (μA) at the Schaffer collateral-CA1 synapses of hippocampal slices from control (n = 7) and stressed (n = 8) rats. **(B)** Input–output curve of NMDA-receptor-mediated fEPSP (fEPSP$_{NMDA}$)(mV × ms) vs stimulus intensity (μA) at the Schaffer collateral-CA1 synapses of hippocampal slices from control (n = 4) and stressed (n = 5) rats. Field EPSP$_{NMDA}$ was recorded in the presence of 10 μ*M* of CNQX, 0.5 m*M* of Mg^{2+}, and 20 μ*M* of bicuculline methchloride. **(C)** The magnitude of the NMDA-receptor-mediated component of EPSCs (EPSC$_{NMDA}$) was estimated by the amplitude of the synaptic currents measured 50 ms after the start of the EPSC and expressed relative to the magnitude of the AMPA receptor component (EPSC$_{AMPA}$) estimated by the size of the EPSC measured 5 ms after the start of the EPSC. The ratio of EPSC$_{NMDA}$ to EPSC$_{AMPA}$ in the CA1 pyramidal cells from stressed rats (n = 5) was not different from that observed in control rats (n = 4) at holding potential of –80 mV and +40 mV. **(D)** LTP was induced by two trains of 100-Hz stimuli in slices pretreated with D-(–)-2-amino-5-phosphonopentanoic acid (D-APV) (50 μ*M*) for 30 min before transferring to recording chamber. Compared with control rats, the ability of stressed rats to induce LTP remained impaired in slices obtained from D-APV treatment.

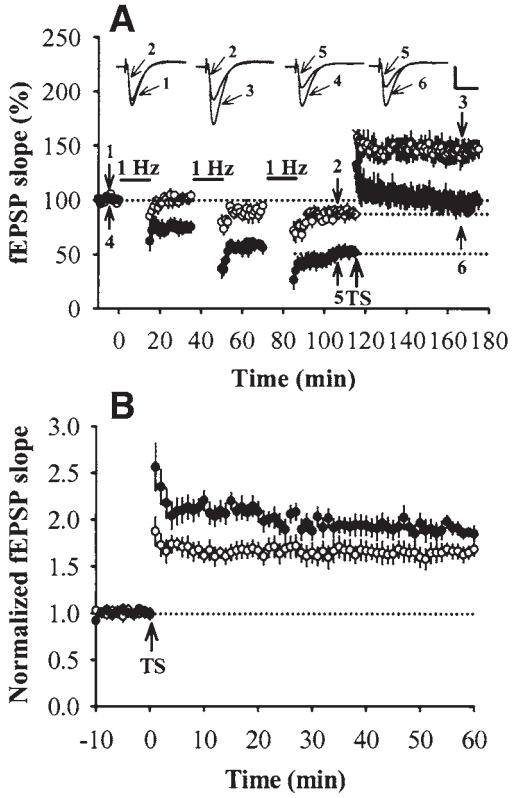

Fig. 2. High-frequency tetanic stimulation-induced LTP deficit in slices from stressed rats was reversed by prior repeated LFS application. **(A)** The recordings of slices from stressed rats (●) displayed a stepwise decline with every additional LFS and the depression was significantly larger than that of control rats (○). After LFS-induced LTD was established, two 1-s trains of 100-Hz stimuli elicited equal levels of LTP in slices from control and stressed rats. **(B)** Data were taken from **(A)** were renormalized to the 10-min period preceding the application of tetanus. (Data adapted from ref. *14*.)

The extracellular signal-regulated kinase1/2 mitogen-activated protein kinase (ERK1/2 MAPK) signaling is a highly conserved kinase cascade linking the transmembrane receptors to downstream effector mechanisms *(32)*. It has been reported that neuronal ERK1/2 MAPK activation is correlated with, and necessary for, long-term taste memory in the insular cortex *(33)*, long-term contextual and auditory fear memory in the amygdala *(34,35)*, and different hippocampal learning paradigms such as contextual fear conditioning *(34)*, spatial learning *(36,37)*, and LTP *(38)*. In addition to its role in synaptic plasticity and various forms of memory formation, stressful spatial learning paradigms have been reported to increase the ERK2 MAPK activation in both hippocampus and amygdala *(39)*. The complex pattern of ERK1/2 MAPK in regulating cognitive functions appears to be relevant to the magnitude and duration of their activation. In the case of learning-related ERK1/2 MAPK activation, it begins immediately following the stimulus, reaches its maximal peak between 1 and 10 min, and returns to baseline 20 min after the initial stimulus *(40)*. Conversely, stress induced a prolonged ERK1/2 MAPK more than several hours after the exposure *(41)*.

Recent findings from our laboratory demonstrated a parallel in time-course of the increased ERK1/2 MAPK activation as well as the effects of stress on LTP and LTD; additionally, a pharmacological blockade of ERK1/2 MAPK signaling cascade completely prevented the stress effects, strongly suggesting a critical role of sustained activation of ERK1/2 MAPK in mediating the blockade of LTP and the facilitation of LTD induced by stress. Consistent with these findings, it has been shown that acute behavioral stress increases the circulating corticosterone levels, leading to the activation of specific glucocorticoid receptors. This results in provocation of the synthesis and release of brain-derived neurotrophic factor (BDNF) acting on tyrosine kinase B (TrkB) receptor to activate a sequential kinase cascade, including protein kinase C (PKC), Ras/Raf-1, MAPK kinase (MEK)1/2, and ERK1/2 MAPK. The activated ERK1/2 MAPK drives its downstream signaling compartments, impairs the LTP induction, and promotes the induction of LTD (Fig. 3). Therefore, these observations provide support for the hypothesis that stress and LTP may exert their effects on common processes.

A pressing issue derived from these observations deals with which downstream targets of ERK1/2 MAPK mediate the stress effects. Because the activated ERK1/2 MAPK can pro-

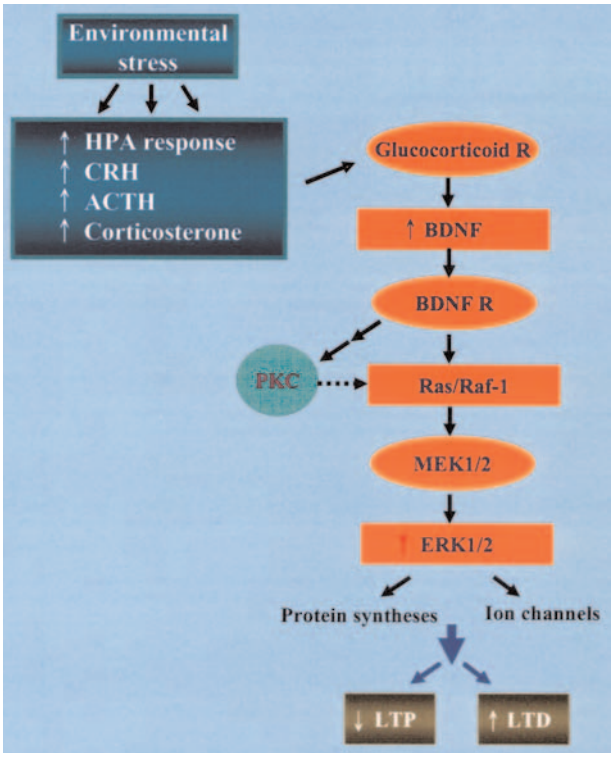

Fig. 3. Model showing possible mechanisms underlying the effects of stress on the subsequent induction of hippocampal CA1 LTP and LTD. Autonomic signals conveying acute stressful stimuli reach the hypothalamus, releasing corticotropin-releasing hormone (CRH) from paraventricular nucleus to influence rapid secretion of ACTH. ACTH induces secretion of corticosterone from adrenal glands, and these interact with glucocorticoids receptors in the hippocampus, thereby initiating signal transduction and leading to provacationof the synthesis and release of BDNF. The increased BDNF subsequently acts on specific TrkB receptors on the hippocampal neurons and, therefore, results in a sustained activation of ERK1/2 MAPK signaling cascade through a mechanism involving the sequential PKC, Ras/Raf-1, and MEK1/2 activation. The activated ERK1/2 MAPK activates some ion channels or protein syntheses; these ion channels or protein syntheses are important components of the machinery required to support LTP, which then occlude LTP and facilitate LTD induction.

mote the activation of many ion channels, neurotransmitter receptors, protein kinases, and transcription factors, the potential candidates are numerous, and it is likely that multiple substrates are involved. Although the precise targeting substrates for ERK1/2 MAPK remain to be determined, the most promising candidates are A-type K^+ channel Kv4.2 and cyclic adenine monophosphate response element binding proteins, which can be regulated by ERK1/2 MAPK-mediated phosphorylation and play a key role in regulating the induction of hippocampal CA1 LTP *(42–44)*. Further work involving the use of functional knockouts of candidate proteins or proteomic approach is needed to address this issue.

Additional supporting evidence for the hypothesis that stress and LTP exert their effects through common processes comes from observations showing that both stress and LTP facilitate LTD induction *(12–14,45,46)*. Recent work has shown that the facilitation of stress on subsequent hippocampal CA1 LTD induction is mediated through the activation of glucocorticoid receptors, leading to the blockade of glutamate uptake and, subsequently, resulting in enhanced spillover of synaptically released glutamate by LFS acting on the extrasynaptic NR2B-containing NMDA receptors to undergo the induction of LTD *(15)*. Additional experiments are necessary to determine whether the same molecular mechanisms are responsible for the induction of the reversal of LTP (depotentiation) in the hippocampal CA1 region, although it has been demonstrated that the induction of depotentiation in the adult perirhinal cortex relies on the activation of NR2A-containing NMDA receptors *(47)*.

Does Stress Induce Metaplastic Effects on the Hippocampal Synaptic Plasticity?

This section reviews experimental evidences and questions regarding the hypothesis that an induction of metaplastic effects contributes to the stress effects on hippocampal synaptic plasticity. Changes in threshold for the induction of synaptic plasticity may also contribute

to the effects of stress on LTP and LTD induction. It is well-established that the direction and magnitude of a synaptic change evoked by a given stimulus depend on the recent history of synaptic and cellular activity. This activity-dependent modulation of subsequent synaptic plasticity has been termed as "metaplasticity" *(48,49)*. The metaplasticity has been suggested to play a crucial role in maintaining synaptic strength within a dynamic range that is optimal for the learning process; additionally, it is suggested to provide a mechanism for integrating synaptic events across periods of time that are orders of magnitude longer than the tens of miniseconds typical of temporal summation of synaptic potentials *(50)*.

The most prominent theoretical model directly relating to metaplasticity is the Bienenstock, Cooper, and Munro (BCM) model of experience-dependent synaptic plasticity, which is designed to account for the plasticity of visual cortex synapses during development *(51)* but may also be relevant to the synaptic models of learning in the hippocampus *(52)*. The main feature of the BCM model is that the stimulation threshold (θ_m) for synaptic modification is not fixed but, rather, is dynamically changed as a function of overall activity levels in the neuronal networks. Therefore, after a period of increased activity, θ_m shifts to the right, promoting synaptic depression. After a period of decreased activity, θ_m shifts to the left, promoting synaptic potentiation. This feature is necessary for the pattern of synaptic strength to reach a stable state.

Abraham and Tate *(49)* and Kim and Yoon *(2)* proposed that the effects of stress on hippocampal synaptic plasticity arise through a shifting of θ_m. These investigators noted that activation of glucocorticoid receptors in the CA1 region of hippocampal slices effectively shifts θ_m to the right *(53)*. The net effect of this right shift is to increase the probability of LTD induction across a wider set of stimulation parameters and to make LTP more difficult to elicit. Because the modulations of glucocorticoid receptor activation on subsequent LTP and LTD induction are similar to the changes

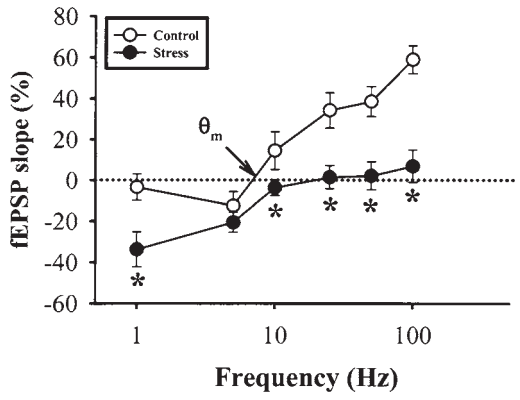

Fig. 4. Frequency–response functions in slices from control and stressed rats. The percentage change in synaptic strength from baseline in all slices was measured at 50 min after stimulation at the indicated frequencies. Note that stress does not cause a significant shift of the functional θ_m relating stimulation frequency in the CA1 region of rat hippocampus.

in synaptic plasticity that occur following stress *(12)*, they proposed that a metaplastic shifting of θ_m to the right may account for the effects of stress on LTP and LTD induction. It is important to note that although Kim et al. *(12)* showed that stress impairs LTP induction and enhances LTD induction, it remains unclear how stress alters the frequency–response profile—mainly because only two stimulation parameters were used in this study. Therefore, it requires a detailed examination across a wide range of stimulation parameters.

Our recent work has provided convincing evidence against this θ_m-shifting hypothesis. As summarized in Fig. 4, our results indicate that stress alters the inducibility for synaptic modification at the Schaffer collateral-CA1 synapses. The frequency–response function for the slices from stressed rats favors LTD at frequencies below 5 Hz stimuli and obliterates LTP induction at frequencies above 10 Hz. We found no evidence that stress causes a right shift in the frequency–response curve. Rather, our data suggest that stress modulates LTP and LTD independently, thereby producing an apparent downward shift in the curve. The

reason for the discrepancy between the effect of glucocorticoid receptor activation and acute stress on the frequency–response profile is not clear but may be partly attributable to the involvement of other neurochemical or endocrine systems in the effects of stress on the hippocampal synaptic plasticity *(54)*.

Do the metaplastic effects of stress on hippocampal synaptic plasticity arise through the persistent activation of NMDA receptors? Because NMDA receptor activation is critical for most forms of synaptic plasticity, a reasonable hypothesis is that changes in NMDA receptor function may be a mechanism underlying the effects of stress on synaptic plasticity. Consistent with this view, it has been shown that the modulations of the induction of both LTP and LTD in the hippocampal CA1 region can be prevented by the administration of NMDA receptor antagonist prior to the stressful experience *(12)*. This feature of stress shares similarities with LTP as well as LTD induction, although the degree of NMDA receptor activation of these forms of plasticity may be quite distinct. The dependence of stress-induced impairment of LTP on NMDA receptor activation raises a possibility that LTP impairment and LTD facilitation observed in stress animals or in the slices from stressed animals may be attributable to the persistent activation of NMDA receptors.

We recently investigated this possibility in vitro by pretreating the hippocampal slices obtained from both control and stressed animals with D-(–)-2-amino-5-phosphonopentanoic acid (D-APV) (50 μ*M*) for 30 min to eliminate the confounded NMDA-receptor-dependent synaptic modifications (Fig. 1D). After washout of D-APV for more than 30 min, high-frequency tetanic stimulation application to slices from control rats, but not in slices from stressed rats, resulted in a reliable LTP, indicating that LTP impairment observed in the slices from stressed rats cannot account for the persistent activation of NMDA receptors following stress.

Corticosterone has been shown to affect the intrinsic membrane properties of hippocampal neurons. For example, Coussens et al. *(53)* and Kerr et al. *(55)* demonstrated that activation of glucocorticoid receptor by corticosterone enhances the slow afterhyperpolarization (AHP) via an increase of the Ca^{2+} currents through voltage-dependent Ca^{2+} channels, thereby activating Ca^{2+}-activated K^+ channels. Because an elevation in intracellular Ca^{2+} ($[Ca^{2+}]_i$) can translate into synaptic modifications by the actions of a network of protein kinases and phosphatases *(56)* and literature strongly suggests that glucocorticoid receptor occupancy mediates the disruptive effects of major stressors *(3,57)*, it has been suggested that the modulation of Ca^{2+} levels contributes to the metaplastic effects of stress on hippocampal synaptic plasticity *(2)*.

In contrast to the enhancement effect of the glucocorticoid receptor activation on AHP, Weiss et al. *(58)* more recently showed that restraint–tailshock stress decreased both the amplitude of postburst AHP and the spike frequency accommodation in the hippocampal CA1 pyramidal neurons in C57Bl/6 mice. Thus, it appears that in addition to glucocorticoid, other neuromodulators are crucially involved in the modulation of excitability of hippocampal neurons. Hopefully these factors will be considered in future research and a more consistent picture of stress neuromodulation in the hippocampus will emerge. Despite this discrepancy, to our knowledge, there is no direct evidence that a disruption of Ca^{2+} homeostasis can be caused by acute or chronic stress in the hippocampal neurons.

Energetic Crisis Hypothesis

The studies performed by Sapolsky and his colleagues *(59,60)* showed that glucocorticoid can increase hippocampal neuronal vulnerability by disrupting cellular energetics. In such cases, hippocampal neurons fail in the costly task of maintaining synaptic glutamate concentrations in a safe range, eventually resulting in an impairment of the ability of neurons to regulate $[Ca^{2+}]_i$ levels. Because the disruption of Ca^{2+} homeostasis may modify the ability of synapses to undergo strength changes in

response to subsequent episodes of synaptic activity *(47,48)*, it is hypothesized that an energetic crisis may also contribute to the effects of stress on the hippocampal synaptic plasticity *(2)*. If stress exerts LTP impairment and LTD facilitation through disruption of neuronal energetics, then such modulations should be prevented if neurons are supplemented with excessive energy. However, this has not been tested explicitly.

Conclusion

None of the hypotheses discussed in this article (those of LTP-like, metaplasticity, or energetic crisis) provide a complete description of the effects of stress on the hippocampal synaptic plasticity. However, they all provided a framework that helped guide us toward the most relevant issues. Although there appears to be fairly widespread support for the notion that stress affects subsequent hippocampal synaptic plasticity through mechanisms in common with LTP, there is not sufficient evidence for this view. One of the great challenges of this hypothesis is demonstrating that chronic stress produces saturated LTP in vivo *(61)*. Similarly, there is not enough evidence to support the view that stress exerts a metaplastic effect (i.e., shifting of θ_m) through disruption of Ca^{2+} homeostasis to cause the effects of stress on hippocampal synaptic plasticity. The majority of supporting evidence for this view comes from in vitro glucocorticoid studies. Indeed, although glucocorticoids can mediate the effects of major stressor, other neurochemical and endocrine systems might work with glucocorticoids to mediate the effects of stress in vivo. Therefore, this hypothesis must be confirmed by further stress model investigation.

With the advent of gene knockout technology, researchers can produce strains of mice with a disruption in a gene of interest. Through the use of this powerful technology, researchers have more opportunity in the future to understand the molecular mechanisms underlying the stress-induced modulations of hippocampal synaptic plasticity. These findings may provide new insight into the molecular mechanisms underlying stress-related memory disorders which, in turn, might provide novel opportunities for the development of more selective medication that targets these pathways and prevents their malfunction *(3)*.

Acknowledgments

This work was financially supported by research grant from the National Health Research Institute (NHRI-EX93-9215NI) of Taipei, Taiwan.

References

1. McEwen B. S. and Sapolsky R. M. (1995) Stress and cognitive function. *Curr. Opin. Neurobiol*. **5**, 205–216.
2. Kim J. J. and Yoon K. S. (1998) Stress: metaplastic effects in the hippocampus. *Trends Neurosci.* **21**, 505–509.
3. Kim J. J. and Diamond D. M. (2002) The stressed hippocampus, synaptic plasticity and lost memories. *Nat. Rev. Neurosci.* **3**, 453–462.
4. Morris R. G., Garrud P., Rawlins J. N., and O'Keefe J. (1982) Place navigation impaired in rats with hippocampal lesions. *Nature* **297**, 681–683.
5. Phillips R. G. and LeDoux J. E. (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.* **106**, 274–285.
6. Squire L. R. and Zola S. M. (1996) Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. USA* **93**, 13,515–13,522.
7. Foy M. R., Stanton M. E., Levine S., and Thompson R. F. (1987) Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav. Neural Biol.* **48**, 138–149.
8. Shors T. J., Seib T. B., Levine S., and Thompson R. F. (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. *Science* **244**, 224–226.
9. Shors T. J. and Dryver E. (1994) Effect of stress and long-term potentiation (LTP) on subse-

quent LTP and the theta burst response in the dentate gyrus. *Brain Res.* **666**, 232–238.
10. Shors T. J., Gallegos R. A., and Breindl A. (1997) Transient and persistent consequences of acute stress on long-term potentiation (LTP), synaptic efficacy, theta rhythms and bursts in area CA1 of the hippocampus. *Synapse* **26**, 209–217.
11. Diamond D. M., Fleshner M., and Rose G. M. (1994) Psychological stress repeatedly blocks hippocampal primed burst potentiation in behaving rats. *Behav. Brain Res*. **62**, 1–9.
12. Kim J. J., Foy M. R., and Thompson R. F. (1996) Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. *Proc. Natl. Acad. Sci. USA* **93**, 4750–4753.
13. Xu L., Anwyl R., and Rowan M. J. (1997) Behavioural stress facilitates the induction of long-term depression in the hippocampus. *Nature* **387**, 497–500.
14. Yang C. H., Huang C. C., and Hsu K. S. (2004) Behavioral stress modifies hippocampal synaptic plasticity through corticosterone-induced sustained extracellular signal-regulated kinase/mitogen-activated protein kinase activation. *J. Neurosci.* **24**, 11,029–11,034.
15. Yang C. H., Huang C. C., and Hsu K. S. (2005) Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake. *J. Neurosci.*, **27,** 4288–4293.
16. Diamond D. M., Park C. R., and Woodson J. C. (2004) Stress generates emotional memories and retrograde amnesia by inducing an endogenous form of hippocampal LTP. *Hippocampus* **14**, 281–291.
17. Garcia R., Musleh W., Tocco G., Thompson R. F., and Baudry M. (1997) Time-dependent blockade of STP and LTP in hippocampal slices following acute stress in mice. *Neurosci. Lett.* **233**, 41–44.
18. Pavlides C., Nivon L. G., and McEwen B. S. (2002) Effects of chronic stress on hippocampal long-term potentiation. *Hippocampus* **12**, 245–257.
19. Diamond D. M., Bennett M. C, Stevens K. E., Wilson E. L., and Rose G. M. (1990) Exposure to a novel environment interferes with the induction of hippocampal primed burst potentiation in the behaving rat. *Psychobiology* **18**, 273–281.
20. Mesches M. H., Fleshner M., Heman K. L., Rose G. M., and Diamond D. M. (1999) Exposing rats to a predator blocks primed burst potentiation in the hippocampus *in vitro*. *J. Neurosci.* **19**, RC18.
21. Xu L., Holscher C., Anwyl R., and Rowan M. J. (1998) Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. *Proc. Natl. Acad. Sci. USA* **95**, 3204–3208.
22. Pavlides C., Watanabe Y., Magarinos A.M., and McEwen B.S. (1995) Opposing roles of type I and type II adrenal steroid receptors in hippocampal long-term potentiation. *Neuroscience* **68**, 387–394.
23. Yamada K., McEwen B. S., and Pavlides C. (2003) Site and time dependent effects of acute stress on hippocampal long-term potentiation in freely behaving rats. *Exp. Brain Res.* **152**, 52–59.
24. Huang Y. Y., Colino A., Selig D. K., and Malenka R. C. (1992) The influence of prior synaptic activity on the induction of long-term potentiation. *Science* **255**, 730–733.
25. Kim J. J., Lee H. J., Han J. S., and Packard M. G. (2001) Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *J. Neurosci.* **21**, 5222–5228.
26. Kim J. J., Koo J. W., Lee H. J., and Han J. S. (2005) Amygdalar inactivation blocks stress-induced impairments in hippocampal long-term potentiation and spatial memory. *J. Neurosci.* **25**, 1532–1539.
27. Diamond D. M., Bennett M. C., Stevens K. E., Wilson R. L., and Rose G. M. (1990) Exposure to a novel environment interferes with the induction of hippocampal primed burst potentiation in the behaving rat. *Psychobiology* **18**, 273–281.
28. Shors T. J. and Thompson R. F. (1992) Acute stress impairs (or induces) synaptic long-term potentiation (LTP) but does not affect paired-pulse facilitation in the stratum radiatum of rat hippocampus. *Synapse* **11**, 262–265.
29. Sacchetti B., Lorenzini C. A., Baldi E., et al. (2001) Long-lasting hippocampal potentiation and contextual memory consolidation. *Eur. J. Neurosci.* **13**, 2291–2298.
30. Huang C. C. and Hsu K. S. (2001) Progress in understanding the factors regulating reversibility of long-term potentiation. *Rev. Neurosci.* **12**, 51–68.
31. Zhou Q. and Poo M. M. (2004) Reversal and consolidation of activity-induced synaptic modifications. *Trends Neurosci.* **27**, 378–383.
32. Chang L. and Karin M. (2001) Mammalian MAP kinase signalling cascades. *Nature* **410**, 37–40.

33. Berman D. E., Hazvi S., Rosenblum K., Seger R., and Dudai Y. (1998) Specific and differential activation of mitogen-activated protein kinase cascades by unfamiliar taste in the insular cortex of the behaving rat. *J. Neurosci.* **18**, 10,037–10,044.
34. Atkins C. M., Selcher J. C., Petraitis J. J., Trzaskos J. M., and Sweatt J. D. (1998) The MAPK cascade is required for mammalian associative learning. *Nat. Neurosci.* **1**, 602–609.
35. Schafe G. E., Nadel N. V., Sullivan G. M., Harris A., and LeDoux J. E. (1999) Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase. *Learn. Mem.* **6**, 97–110.
36. Blum S., Moore A. N., Adams F., and Dash P. K. (1999) A mitogen-activated protein kinase cascade in the CA1/CA2 subfield of the dorsal hippocampus is essential for long-term spatial memory. *J. Neurosci.* **19**, 3535–3544.
37. Selcher J. C., Atkins C. M., Trzaskos J. M., Paylor R., and Sweatt J. D. (1999) A necessity for MAP kinase activation in mammalian spatial learning. *Learn. Mem.* **6**, 478–490.
38. English J. D. and Sweatt J. D. (1996) Activation of p42 mitogen-activated protein kinase in hippocampal long term potentiation. *J. Biol. Chem.* **271**, 24,329–24,332.
39. Akirav I., Sandi C., and Richter-Levin G. (2001) Differential activation of hippocampus and amygdala following spatial learning under stress. *Eur. J. Neurosci.* **14**, 719–725.
40. Davis S., Vanhoutte P., Pages C., Caboche J., and Laroche S. (2000) The MAPK/ERK cascade targets both Elk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus *in vivo*. *J. Neurosci.* **20**, 4563–4572.
41. Trentani A., Kuipers S. D., Ter Horst G. J., and Den Boer J. A. (2002) Selective chronic stress-induced in vivo ERK1/2 hyperphosphorylation in medial prefrontocortical dendrites: implications for stress-related cortical pathology? *Eur. J. Neurosci.* **15**, 1681–1691.
42. Adams J. P., Roberson E. D., English J. D., Selcher J. C., and Sweatt J. D. (2000) MAPK regulation of gene expression in the central nervous system. *Acta Neurobiol. Exp.* **60**, 377–394.
43. Morozov A., Muzzio I. A., Bourtchouladze R., et al. (2003) Rap1 couples cAMP signaling to a distinct pool of p42/44MAPK regulating excitability, synaptic plasticity, learning, and memory. *Neuron* **39**, 309–325.
44. Impey S., Mark M., Villacres E. C., Poser S., Chavkin C., and Storm D. R. (1996) Induction of CRE-mediated gene expression by stimuli that generate long-lasting LTP in area CA1 of the hippocampus. *Neuron* **16**, 973–982.
45. Barrionuevo G., Schottler F., and Lynch G. (1980) The effects of repetitive low frequency stimulation on control and "potentiated" synaptic responses in the hippocampus. *Life Sci*. **27**, 2385–2391.
46. Fujii S., Saito K., Miyakawa H., Ito K., and Kato H. (1991) Reversal of long-term potentiation (depotentiation) induced by tetanus stimulation of the input to CA1 neurons of guinea pig hippocampal slices. *Brain Res*. **555**, 112–122.
47. Massey P. V., Johnson B. E., Moult P. R., et al. (2004) Differential roles of NR2A and NR2B-containing NMDA receptors in cortical long-term potentiation and long-term depression. *J. Neurosci*. **24**, 7821–7828.
48. Abraham W. C. and Bear M. F. (1996) Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* **19**, 126–130.
49. Abraham W. C. and Tate W. P. (1997) Metaplasticity: a new vista across the field of synaptic plasticity. *Prog. Neurobiol*. **52**, 303–323.
50. Abraham W. C. (1999) Metaplasticity: Key Element in Memory and Learning? *News Physiol. Sci.* **14,** 85.
51. Bienenstock E. L., Cooper L. N., and Munro P. W. (1982) Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J. Neurosci.* **2**, 32–48.
52. Bear M. F. (1995) Mechanism for a sliding synaptic modification threshold. *Neuron* **15**, 1–4.
53. Coussens C. M., Kerr D. S., and Abraham W. C. (1997) Glucocorticoid receptor activation lowers the threshold for NMDA-receptor-dependent homosynaptic long-term depression in the hippocampus through activation of voltage-dependent calcium channels. *J. Neurophysiol*. **78**, 1–9.
54. McGaugh J. L., Cahill L., and Roozendaal B. (1996) Involvement of the amygdala in memory storage: interaction with other brain systems. *Proc. Natl. Acad. Sci. USA* **93**, 13508–13514.
55. Kerr D. S., Campbell L. W., Hao S. Y., and Landfield P. W. (1989) Corticosteroid modulation of hippocampal potentials: increased effect with aging. *Science* **245**, 1505–1509.
56. Bear M. F. and Malenka R. C. (1994) Synaptic plasticity: LTP and LTD. *Curr. Opin. Neurobiol*. **4**, 389–399.

57. Lupien S. J. and McEwen B. S. (1997) The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Res. Brain Res. Rev.* **24**, 1–27.
58. Weiss C., Sametsky E., Sasse A., Spiess J., and Disterhoft J. F. (2005) Acute stress facilitates trace eyeblink conditioning in C57BL/6 male mice and increases the excitability of their CA1 pyramidal neurons. *Learn. Mem.* **12**, 138–143.
59. Lawrence M. S. and Sapolsky R. M. (1994) Glucocorticoids accelerate ATP loss following metabolic insults in cultured hippocampal neurons. *Brain Res.* **646**, 303–306.
60. Sapolsky R. M. (1996) Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. *Stress* **1**, 1–19.
61. Abraham W. C. (2004) Stress-related phenomena. *Hippocampus* **14**, 675, 676.