

## CHAPTER 8

# Synaptic plasticity in learning and memory: stress effects in the hippocampus

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**Abstract:** Synaptic plasticity has often been argued to play an important role in learning and memory. The discovery of long-term potentiation (LTP) and long-term depression (LTD), the two most widely cited cellular models of synaptic plasticity, significantly spurred research in this field. Although correlative evidence suggesting a role for synaptic changes such as those seen in LTP and LTD in learning and memory has been gained in a number of studies, definitive demonstrations of a specific role for either LTP or LTD in learning and memory are lacking. In this review, we discuss a number of recent advancements in the understanding of the mechanisms that mediate LTP and LTD in the rodent hippocampus and focus on the use of subunit-specific *N*-methyl-D-aspartate receptor antagonists and interference peptides as potential tools to study the role of synaptic plasticity in learning and memory. By using the modulation of synaptic plasticity and hippocampal-dependent learning and memory by acute stress as an example, we review a large body of convincing evidence indicating that alterations in synaptic plasticity underlie the changes in learning and memory produced by acute stress.

**Keywords:** glutamate; NR2B; interference peptide; water maze; LTP; LTD; endocytosis; AMPA; NMDA; GluR2

### Introduction: synaptic plasticity, learning, and memory

The theory postulating that changes at synapses within the brain underlie learning and memory (along with many other behavioral phenomena) was formalized by Donald Hebb in his seminal work *The Organization of Behavior: A Neuropsychological Theory* (Hebb, 1949). Since that time, strong support for his theory has been gained through a

number of lines of research. Most important in this regard is likely the discovery of synaptic long-term potentiation (LTP) and long-term depression (LTD) within the mammalian hippocampus (Bliss and Lomo, 1973; Lynch et al., 1977; Dudek and Bear, 1992; Bliss and Collingridge, 1993; Bear and Abraham, 1996; Malenka and Nicoll, 1999). Intense interest has focused on these forms of synaptic plasticity as they have a number of properties that make them suitable as models for the synaptic changes that likely occur during learning and memory. The classic properties of LTP including input specificity, associative induction, and persistence are key examples of such properties

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and have been discussed extensively elsewhere (Bliss and Collingridge, 1993; Martin et al., 2000).

Since the discovery of LTP and LTD, rigorous experiments have been conducted that support the role of synaptic plasticity in learning and memory. Changes in synaptic plasticity have been observed for different types of memory which depend on discrete neural circuits including the hippocampus and amygdala (Martin et al., 2000; Sigurdsson et al., 2007). Most of these experiments have focused on the potential role of LTP-like plasticity in learning and memory using normal (Rogan et al., 1997; Pastalkova et al., 2006; Whitlock et al., 2006) or genetically modified rodents (Mayford et al., 1996; Tang et al., 1999), however, a lack of specific inhibitors for either LTP or LTD has hindered progress in determining the specific types of synaptic plasticity involved in various forms of learning and memory.

Importantly, numerous experiential factors, such as acute stress, have profound effects on learning and memory which are correlated with altered synaptic plasticity in relevant brain areas (Kim et al., 2006). A number of recent advancements in understanding the mechanisms through which stress affects synaptic plasticity have shed new light on how altered synaptic plasticity may affect behavior. The present review focuses on these advancements as an example of the critical role of synaptic plasticity in the biological basis of learning and memory. In this review, we begin by summarizing recent advancements in understanding the mechanisms of *N*-methyl-D-aspartate glutamate receptor (NMDAR)-mediated LTP and LTD in the CA1 area of the hippocampus and continue with a detailed discussion of number of recent studies that have examined the contribution of these mechanisms to the effects of acute stress on learning and memory. The implications of these findings for current theories of synaptic plasticity and memory are also discussed.

### **Mechanisms underlying synaptic plasticity in the hippocampus**

Research into the mechanisms underlying LTP and LTD in the CA1 region of the hippocampus is

especially vigorous (Malenka and Nicoll, 1999; Malenka and Bear, 2004). However, determining the specific alterations in synaptic plasticity that are critical for learning and memory has been hindered by a lack of specific inhibitors of LTP and LTD. The recent discovery of a number of compounds that may be suitable for specifically targeting LTP or LTD in behaving animals has provided potential new avenues for research in this area. The following section will review evidence regarding the usefulness of these compounds for understanding the potential link between synaptic plasticity and learning and memory.

### ***Induction of LTP/LTD***

It is generally well accepted that the induction of hippocampal CA1 homosynaptic LTP and LTD depends on the activation of NMDARs (Bliss and Collingridge, 1993; Malenka and Bear, 2004). NMDARs are heteromeric complexes of NR1 subunits, at least one type of NR2 subunits (NR2A-D), and NR3 (A or B) subunits in some areas (Cull-Candy et al., 2001; Paoletti and Neyton, 2007). NMDARs have a number of unique characteristics which make them particularly attractive as a molecular substrate mediating the induction of synaptic plasticity. For example, under conditions of low post-synaptic activity, NMDARs are blocked in a voltage-dependent manner by magnesium ions. When post-synaptic activity is high, such as under conditions suitable for producing plasticity, the post-synaptic membrane depolarizes enough to remove the magnesium block. Once activated, NMDARs are also highly permeable to calcium ions. Importantly, the post-synaptic influx of calcium is a critical step underlying both LTP and LTD, although the detailed mechanisms surrounding calcium influx that give rise to either LTP or LTD is still the subject of significant debate (Malenka and Bear, 2004).

Converging evidence supports the hypothesis that the subunit composition of NMDARs confers distinct roles of the receptors in normal and pathological brain function (Cull-Candy et al., 2001; Paoletti and Neyton, 2007). The development of NMDAR subunit-selective pharmacological agents such as NVP-AAM077 (Auberson et al.,

2002) for NR2A-containing receptors and Ro25-6981 (Mutel et al., 1998) for NR2B-containing receptors has made it possible to test this hypothesis. Several studies using these compounds in *in vitro* brain slices prepared from both young and adult rodents provide evidence for a critical role of NR2A-containing NMDAR activation in hippocampal CA1 LTP (Liu et al., 2004) and NR2B-containing NMDARs activation in the induction of hippocampal CA1 LTD (Liu et al., 2004; Woo et al., 2005; Yang et al., 2005; Izumi et al., 2006). Similar results have also been obtained in slices from the perirhinal cortex of young adult rats (Massey et al., 2004).

However, contradictory results have been reported by others (Hendricson et al., 2002; Berberich et al., 2005; Morishita et al., 2007). Since results both for and against a critical involvement of NR2B-containing receptors in LTD were independently obtained from more than one laboratory, it is possible that the subunit requirements for LTD are state-dependent phenomena and these contradictory results may be due in part to different conditions used in the *in vitro* studies. Additionally, the subunit specificity of NVP-AAM077 for NR2A- versus NR2B-containing receptors may be less than originally reported, especially when rat recombinant NMDA receptors are used for the binding assays (Frizelle et al., 2006). Therefore, further validation of the role of NR2A-containing receptors in synaptic plasticity awaits the development of a new generation of NR2A antagonists with better pharmacological subunit specificity. Determining the exact roles of NMDAR subunits in synaptic plasticity is also complicated by the potential existence of native NMDAR complexes of NR1/NR2A/NR2B subunits (Sheng et al., 1994). Such trimeric receptor complexes would likely have pharmacological properties that differ from either NR1/NR2A or NR1/NR2B dimeric complex. However, using quantitative immunoprecipitation techniques, Al-Hallaq et al. (2007) have recently reported that the majority of native NMDARs in the rat hippocampus are di-heteromeric receptors containing either NR1/NR2A or NR1/NR2B subunits.

Importantly, the subunit specificity of NMDAR-dependent LTP and LTD originally reported in

*in vitro* studies has recently been corroborated by *in vivo* studies. Thus, within the narrow range of concentrations used, NVP-AAM077 and Ro25-6981 were shown to preferentially inhibit hippocampal CA1 LTP and LTD, respectively, in anesthetized rats (Fox et al., 2006). Although these findings remain to be confirmed by other laboratories and extended to other brain areas, such preferential inhibition of either LTP or LTD with NMDAR subunit-specific antagonists *in vivo* offers a valuable opportunity to use these drugs to begin to probe the specific roles of LTP and/or LTD in mediating some aspects of learning and memory (Duffy et al., 2007; Wong et al., 2007). A number of experiments designed to address this question will be further described in the section discussing the effects of stress on synaptic plasticity and learning and memory.

### *Expression of LTP/LTD*

Although the activation of NMDARs is required for the induction of LTP and LTD (Malenka and Bear, 2004), the expression of these forms of synaptic plasticity is likely dependent on both presynaptic changes in transmitter release and post-synaptic changes in the  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid subtype of glutamate receptors (AMPA; Malenka and Nicoll, 1999; Collingridge et al., 2004; Malenka and Bear, 2004). AMPARs mediate the majority of the fast synaptic transmission in the mammalian brain and are generally expressed as tetramers composed of various patterns of four subunits (GluR1-4; Derkach et al., 2007). Although modifications to pre-existing AMPARs likely contribute to various forms of synaptic plasticity, considerable research also suggests receptor trafficking (rapid changes in the number of AMPARs) plays an important role in LTP and LTD (Collingridge et al., 2004; Derkach et al., 2007). Strong support for the insertion and endocytosis of AMPARs during LTP and LTD, respectively, has been gained using a number of methods *in vitro* (Ahmadian et al., 2004; Derkach et al., 2007). Clearly, a more thorough understanding of the molecular mechanisms underlying receptor trafficking in synaptic plasticity may have important relevance for determining the

precise roles of different forms of synaptic plasticity in learning and memory.

A large body of evidence has accumulated in recent years strongly supporting an important role of clathrin-mediated endocytosis of post-synaptic AMPARs in the expression of hippocampal CA1 LTD (Carroll et al., 1999; Man et al., 2000) and cerebellar LTD (Wang and Linden, 2000). The endocytosis of AMPARs during LTD is specifically associated with those receptors containing at least one GluR2 subunit (Luscher et al., 1999; Man et al., 2000; Wang and Linden, 2000; Lee et al., 2002). Several studies have revealed that the GluR2 subunit-specificity is mediated by several sequence motifs in the carboxyl tail (CT) region of the subunit, including a motif located in the middle of the CT that binds to both NSF and the AP-2 clathrin adaptor. A PDZ-binding motif at the end of the CT also interacts with a number of PDZ-containing proteins such as GRIP, ABP, and PICK1 (Collingridge et al., 2004). In addition, a novel tyrosine phosphorylation-dependent endocytic motif in the GluR2 CT that is absolutely required for regulated AMPAR endocytosis has been identified using a systematic mutational analysis (Ahmadian et al., 2004; Hayashi and Huganir, 2004). Given that interfering with any of these motifs blocks activity-dependent AMPAR endocytosis, and hence various forms of LTD (Kim et al., 2001; Lee et al., 2002; Chung et al., 2003; Ahmadian et al., 2004; Brebner et al., 2005), all these motifs are likely functional and indispensably involved in regulated AMPAR endocytosis in neurons.

Additional mechanisms involving AMPAR subunits other than GluR2 have been demonstrated to differentially regulate synaptic plasticity and may also be important for AMPAR endocytosis. For example, the major phosphorylation sites for protein kinase A (P<sub>845</sub>) and calcium/calmodulin-dependent protein kinase II (P<sub>831</sub>) on GluR1 subunits are differentially regulated during the induction of LTP and LTD (Lee et al., 2000) and are required for the retention of spatial memory in the water maze (Lee et al., 2003). Interestingly, cultured neurons from mice with knock-in mutations at both phosphorylation sites show reduced NMDA-induced GluR1 internalization, which may

reflect disrupted AMPAR endocytosis (Lee et al., 2003).

Although the mechanisms by which these multiple internalization signals act in concert during various forms of synaptic plasticity remain to be determined, the development of several interference peptides that inhibit regulated AMPAR endocytosis, thereby specifically preventing the expression of LTD without altering LTP, has provided several potentially important tools for probing the specific roles of LTD in behavior (Brebner et al., 2005; Wong et al., 2007). For example, using a tyrosine motif interference peptide (GluR2<sub>3Y</sub>), we have provided the first evidence for a causal role of LTD in the expression of behavioral sensitization, an animal model of drug addiction induced by repeated intermittent administration of drugs of abuse such as amphetamine (Brebner et al., 2005).

The GluR2<sub>3Y</sub> peptide (<sub>869</sub>YKEGYNVYG<sub>877</sub>) was first identified through a systematic deletion and CT truncation in the GluR2 CT (Ahmadian et al., 2004). When delivered into post-synaptic neurons, the synthetic peptide containing this sequence of amino acids blocks LTD by interfering with the facilitated endocytosis of AMPARs, the last step of LTD expression, without affecting any upstream signaling steps (Ahmadian et al., 2004; Brebner et al., 2005). An inactive control peptide, with the 3 critical tyrosine residues mutated to alanines (GluR2<sub>3A</sub>), has no effect on LTD. Further experiments have shown that fusing these peptides with the cell membrane transduction domain of the HIV-1 Tat protein (Schwarze et al., 1999) allows them to be transported across the blood brain barrier and into neurons with systemic or intracranial administration. Once in neurons, the GluR2<sub>3Y</sub> peptide specifically blocks the expression of LTD without affecting LTP (Brebner et al., 2005; Fox et al., 2007). Thus, these interference peptides are particularly well suited for studying the specific role(s) of LTD in various forms of learning and memory *in vivo*.

### Acute stress

Historically in the biological sciences, the term stress has been used to describe the rather vague

range of stimuli or conditions that disturb the homeostasis of an organism (Kim and Diamond, 2002). The stress response involves activation of the hypothalamic–pituitary–adrenal (HPA) axis and release of glucocorticoid stress hormones (cortisol in humans; corticosterone in most rodents) from the adrenal glands and other mediators such as catecholamine neurotransmitters and cytokines. Psychological aspects of an organism's experience of given stimuli or conditions, such as its level of aversiveness or controllability, are also critical in determining whether a given experience is perceived as “stressful” (Kim and Diamond, 2002). In the short term, the stress response results in a number of highly adaptive changes in the body and brain which enable the organism to overcome the period of challenge. However, chronic activation of the stress response has negative effects on a number of physiological systems in the body (Sapolsky, 1992). More recently, Bruce McEwen and his colleagues have used the terms allostasis and allostatic overload to describe the short-term (adaptive) and long-term (maladaptive) effects of stress, respectively (McEwen, 2004, 2005).

Stress has diverse effects on the brain which depend greatly on the characteristics of the stressor experienced and the brain area examined. Limbic structures, such as the hippocampal formation, are strongly influenced by stress for a number of reasons (Sapolsky, 1992; McEwen, 1999). For example, the hippocampal formation is highly enriched with the two types of adrenal steroid receptors (Reul and de Kloet, 1985). Mineralocorticoid (Type I) receptors have a high affinity for glucocorticoids and are generally saturated under basal conditions whereas glucocorticoid (Type II) receptors have a 10-fold lower affinity for glucocorticoids and are only occupied when circulating levels of glucocorticoids are elevated, such as during periods of stress (Reul and de Kloet, 1985). The hippocampus is also critically involved in regulating the responsiveness of the HPA axis through glucocorticoid-mediated negative feedback and is particularly vulnerable to the neurodegenerative effects of chronic stress (Sapolsky, 1992; McEwen and Sapolsky, 1995).

Given the influence of stress on the hippocampus, it should not be surprising that complex effects

of stress on hippocampal synaptic plasticity and cognition have been demonstrated using a variety of paradigms in both human and animal studies. A number of insightful reviews have discussed this literature in considerable detail (Kim and Diamond, 2002; Roozendaal, 2002; Diamond et al., 2004, 2005; Shors, 2004, 2006; Huang et al., 2005; Joels et al., 2006; Kim et al., 2006). However, significant advances in understanding the mechanisms through which stress may affect the physiology of limbic areas and ultimately cognition have been made recently. The remainder of the present review discusses these advances and integrates them into contemporary conceptualizations of the role of synaptic plasticity in learning and memory.

### *Effects of acute stress on hippocampal synaptic plasticity*

In the CA1 region of the hippocampus, acute stress impairs LTP and primed-burst potentiation, a low threshold form of LTP, in vitro (Foy et al., 1987; Shors et al., 1989; Mesches et al., 1999) and in vivo (Diamond et al., 1994; Xu et al., 1997). Additionally, acute stress also enhances LTD in the hippocampus in vitro (Kim et al., 1996; Yang et al., 2005) and in vivo (Xu et al., 1997). These effects on synaptic plasticity occur following a number of stressors including administration of shock (Shors et al., 1989), exposure to a novel environment (Xu et al., 1997), placement on an elevated platform (Xu et al., 1998), or exposure to a predator (Mesches et al., 1999). In an important study, Shors and her colleagues demonstrated that the LTP deficits following stress only occur in rats unable to terminate (or control) their exposure to shock (Shors et al., 1989). Thus, it appears that the effects of the stressor on synaptic plasticity are determined by the psychological factors involved in stress, and not just the physical factors (Kim et al., 2006). Other limbic brain areas, such as the amygdala, are likely critically involved in the effects of stress on hippocampal synaptic plasticity as amygdalar lesions prevent the effects of stress on hippocampal plasticity (Kim et al., 2005).

The cellular mechanisms underlying the effects of acute stress on synaptic plasticity have been studied extensively. It is tempting to speculate that



the effects of stress depend on elevated levels of adrenal hormones; however, the data do not entirely support this hypothesis. Although blocking the activation of glucocorticoid receptors before or immediately following stress blocks the effects of stress on synaptic plasticity (Xu et al., 1998; Yang et al., 2004, 2005), adrenalectomizing rats prior to stress fails to block the disruptive effects of stress on LTP (Shors et al., 1990). Additionally, animals that can terminate administered shocks show elevated levels of corticosterone similar to those animals not able to terminate the shock, but do not show alterations in synaptic plasticity following stress (Shors et al., 1989). Thus, although elevated levels of corticosterone are a critical determinant of the effects of stress on synaptic plasticity, in some cases, the increase in glucocorticoid hormones must interact with other factors to enable stress to alter synaptic plasticity.

Substantial evidence also suggests that the effects of acute stress on synaptic plasticity are mediated by glutamatergic neurotransmission. For example, pretreatment with NMDA antagonists blocks the effects of stress on the induction of both LTP and LTD in the hippocampus (Kim et al., 1996). Interestingly, Yang and colleagues recently showed that exploration of a novel environment following acute stress reverses the expected effects of acute stress on both LTP and LTD (Yang et al., 2006). The novelty effects depend on activation of the cholinergic system and NMDARs, which in turn activate the protein phosphatase 2B and striatal-enriched tyrosine phosphatase. Thus, exposure to certain environmental stimuli which activate NMDARs also reverse the stress-induced changes in hippocampal synaptic plasticity.

Moreover, recent evidence suggests that stress may enable LTD in the CA1 region of the hippocampus by either enhancing the release of glutamate or blocking glutamate reuptake (Lowy et al., 1993, 1995; Yang et al., 2005; Wong et al., 2007). Either of these mechanisms allow for the activation of extra-synaptic NMDARs, which are thought to be comprised mostly of NR2B-containing NMDARs in the adult rodent CA1 region (Hardingham et al., 2002; Yang et al., 2005; Duffy et al., 2007; Wong et al., 2007). Antagonists for NR2B-containing NMDARs are effective at

blocking the induction of LTD following stress (Yang et al., 2005; Fox et al., 2006; Wang et al., 2006; Wong et al., 2007), and may also reverse the stress-induced disruption of LTP (Wang et al., 2006). Thus, it appears that the LTD enabled by stress may share similar mechanisms to LTD induced in the hippocampus without stress in vitro (Liu et al., 2004; Woo et al., 2005; Yang et al., 2005; Izumi et al., 2006). Further support that stress-enabled LTD shares similar mechanisms to LTD induced without stress comes from a recent study reporting that administration of the Tat-GluR2<sub>3Y</sub>, but not the Tat-GluR2<sub>3A</sub>, peptide blocks stress-enabled CA1 LTD in young adult rats in vivo (Fox et al., 2007). Thus, it appears that the expression of stress-enabled LTD is also dependent on the clathrin-dependent endocytosis of GluR2-containing AMPARs.

#### *What is the mechanism through which stress alters synaptic plasticity?*

Significant progress has been made regarding the role of specific alterations in synaptic plasticity caused by acute stress in learning and memory. However, a number of important challenges remain. Most importantly, considerable debate remains regarding the mechanism by which acute stress alters synaptic plasticity in the hippocampus by promoting the induction of LTD and inhibiting the induction of LTP (Kim and Yoon, 1998; Abraham, 2004; Diamond et al., 2004, 2005; Huang et al., 2005). A number of lines of evidence suggest that stress and LTP share common molecular mechanisms and that stress may saturate LTP, thereby inhibiting its induction (Diamond et al., 2004, 2005; Huang et al., 2005). Correlational support for this hypothesis comes from studies showing a number of common effects between stress and the induction of LTP on the activation of immediate early genes, ionotropic glutamate receptors, and learning and memory (see Diamond et al., 2004 for specific references). Direct support for this hypothesis would be gained with a clear demonstration that acute stress increases synaptic potentials in a manner similar to LTP. One study (Sacchetti et al., 2001) provides such support by showing that contextual fear conditioning (which is

inherently stressful) produces a long-lasting increase in the evoked CA1 response in hippocampal slices of fear conditioned rats. However, this finding has not been replicated and no significant changes in evoked responses from the hippocampus have been observed during or immediately following acute stress per se (Xu et al., 1997; Huang et al., 2005).

A second possibility is that stress exerts modulatory effects on synaptic plasticity in the hippocampus by altering the induction threshold for LTP and LTD (Kim and Yoon, 1998; Abraham, 2004; Huang et al., 2005). Such 'metaplastic' changes or alterations in the ability to induce different forms of synaptic plasticity by prior activity are an important characteristic of a number of neural circuits, including the CA1 region of the hippocampus (Abraham and Bear, 1996; Kirkwood et al., 1996; Mockett et al., 2002). The Bienenstock, Cooper, and Munro (BCM) model is a frequently cited computational model designed to explain the modifications that may occur in synaptic plasticity as a result of experience (Bienenstock et al., 1982). One of the central components of the model is that the threshold for plasticity (referred to as  $\theta_m$ ) in a given circuit is not fixed, but rather changes as a result of experience. Thus, as stress favors the induction of LTD over LTP, it could be hypothesized that this results from a rightward shift of  $\theta_m$ . Direct support for the a shift in  $\theta_m$  following stress has been difficult to obtain (Huang et al., 2005), although promising results have been reported following the pharmacological activation of glucocorticoid receptors (Coussens et al., 1997).

### ***Effects of acute stress on hippocampal-based learning and memory***

Acute stress has differential effects on learning and memory that depend on a number of factors including the type of task, timing of the stress, and sex of the subject (Joels et al., 2006; Kim et al., 2006; Shors, 2006). In the present review, we restrict our discussion to spatial memory retrieval deficits following acute stress because recent advancements in this area provide an excellent

example of the consequences of specific changes in synaptic plasticity on learning and memory.

When rodents are trained in spatial memory tasks, such as the water maze or radial arm maze, acute stress does not significantly affect the ability of the animals to learn the task (Diamond et al., 1999; Kim et al., 2005) or the retrieval of hippocampal-independent reference memory (Diamond et al., 1996; Woodson et al., 2003). In contrast, acute stress disrupts the retrieval of hippocampal-dependent spatial memory whether the stress occurs before the learning (Diamond et al., 2006) or retrieval phase of the test (Diamond et al., 1996, 1999; de Quervain et al., 1998). The disruptive effects of acute stress on hippocampal-dependent memory retrieval are particularly robust and have also been demonstrated using a number of paradigms in human (Het et al., 2005; Kuhlmann et al., 2005) and rodent studies (Baker and Kim, 2002). Importantly, these effects can be mimicked by cortisol or corticosterone treatment (de Quervain et al., 1998, 2000, 2003; Het et al., 2005) and are modulated by a number of factors including levels of arousal and emotional valence of the stimuli (Kuhlmann et al., 2005; Kuhlmann and Wolf, 2006a, b). Interestingly, acute stress also enhances memory in aversive hippocampal-dependent tasks such as contextual fear conditioning and trace eye-blink conditioning (Beylin and Shors, 1998; Nijholt et al., 2004), thereby demonstrating that the effects of stress may differ in aversively motivated contexts.

The mechanisms that underlie the effects of stress on spatial memory retrieval have received considerable attention. In an important paper from McGaugh's group (de Quervain et al., 1998), spatial memory retrieval deficits were observed 30 min, but not 2 min or 4 h, after footshock stress. Thirty minutes following stress coincided with the peak level of circulating corticosterone, thereby supporting the notion that increases in corticosterone may cause the memory retrieval deficits. This hypothesis is further supported by the fact that pharmacologically inhibiting corticosterone synthesis blocks the memory retrieval deficits, while administration of corticosterone in the absence of stress induced retrieval deficits (de Quervain et al., 1998).

However, as with the effects of stress on hippocampal synaptic plasticity, increased release of corticosterone cannot fully account for the effects of acute stress on memory retrieval. In a well-designed experiment, Diamond and his colleagues exposed rats to either a cat or a sexually receptive female rat before spatial memory testing (Woodson et al., 2003). Although both stimuli aroused the rats and resulted in similar increases in corticosterone, only the group exposed to the cat displayed disrupted hippocampal-dependent memory. Therefore, similar to the effects of stress on synaptic plasticity, increased release of corticosterone is not sufficient to cause stress-induced memory retrieval deficits.

### ***Roles of LTP and LTD in stress-induced spatial memory impairment***

Other studies have examined the role altered hippocampal glutamatergic synaptic plasticity may play in acute stress-induced spatial memory retrieval impairments. As was reviewed above, acute stress induces a profound shift in the pattern of hippocampal synaptic plasticity by enabling the induction of LTD and blocking the induction of LTP. If the memory retrieval impairments are due to alterations in synaptic plasticity caused by stress, treatments which reverse the effects of stress on synaptic plasticity would be expected to also reverse the memory retrieval impairments. Strong support for this hypothesis has been gained from a number of studies. For example, NMDA antagonists block the enabling and inhibiting effects of acute stress on LTD and LTP, respectively (Kim et al., 1996). Blocking NMDARs with a broad spectrum antagonist (CPP) also reverses the disruptive effects of stress on spatial memory (Park et al., 2004), thereby supporting the conjecture that the disruptive effects of stress on memory retrieval may be a result of NMDAR-dependent alterations in hippocampal synaptic plasticity. It is worth noting that under normal conditions, administration of NMDAR antagonists to unstressed animals disrupts spatial memory retrieval but in this case, NMDA antagonism prevents the effects of stress on spatial memory retrieval by preserving the normal function of the hippocampus (i.e. blocking

LTD and keeping it in an 'LTP' prone state; Diamond et al., 2005).

Although these studies implicate altered synaptic plasticity in the stress-induced impairment of memory, it is unclear whether specific alterations in either LTP or LTD caused by stress are responsible for the stress-induced impairment of spatial memory retrieval. In a recent study, we provide strong evidence for an essential and sufficient role of hippocampal LTD in mediating acute stress-induced impairment of spatial memory retrieval by specifically inhibiting LTD with the structurally and mechanistically distinct inhibitors Ro25-6981 and the Tat-GluR2<sub>3Y</sub> peptide and facilitating the induction of LTD by inhibiting glutamate uptake (Fig. 1; Wong et al., 2007). More specifically, administration of the specific NR2B subunit-containing NMDAR antagonist (Ro25-6981) reversed the disruptive effect of stress on spatial memory retrieval in a water maze task (Wong et al., 2007). Given that Ro25-6981 has been shown convincingly to block stress-enabled LTD (Yang et al., 2005; Fox et al., 2006; Wang et al., 2006; Wong et al., 2007) and reverse the disruption of LTP by stress (Wang et al., 2006), these data suggest that the activation of NR2B-containing receptors are critical for the effects of stress on synaptic plasticity and memory retrieval. Interestingly, the increases in hippocampal glutamate efflux observed after stress can be mimicked pharmacologically by local injections of the glutamate transporter inhibitor DL-TBOA (Wong et al., 2007). Under these conditions, LTD is readily induced in the hippocampus in vivo and spatial memory retrieval is disrupted. Similar to the effects of stress, both the alterations in synaptic plasticity and memory retrieval in TBOA-treated animals can be reversed with Ro25-6981 (Wong et al., 2007). Further support for the essential role of LTD in the spatial memory retrieval disruptions following acute stress is gained from experiments showing that administration of the Tat-GluR2<sub>3Y</sub> peptide, which specifically blocks AMPAR endocytosis and stress-enabled LTD in vivo (Fox et al., 2007), also blocks the disruptive effects of acute stress on spatial memory retrieval (Wong et al., 2007). Taken together, the results of these studies provide convincing support for the hypothesis that



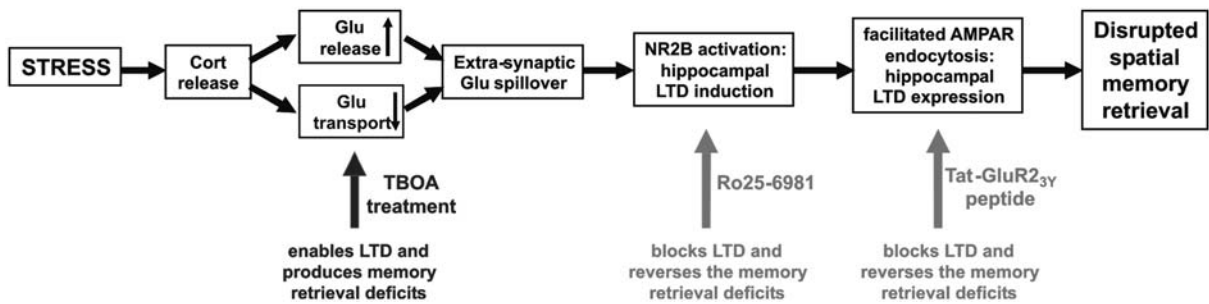


Fig. 1. Schematic describing the hypothetical mechanisms by which acute stress enables induction of long-term depression (LTD) in the hippocampus, thereby causing impaired spatial memory retrieval and the steps at which experimental treatments performed in Wong et al. (2007) interfere with this process. Acute stress causes the release of corticosterone (Cort) which then increases glutamate concentration in the synaptic cleft either through increased glutamate (Glu) release and/or decreased glutamate transport in the hippocampus. The increased glutamate concentration enables the induction of LTD via a spill-over activation of extra-synaptically localized NR2B-containing NMDARs, and hence the expression of LTD via facilitating the endocytosis of post-synaptic AMPARs, thereby leading to the disrupted spatial memory retrieval. The treatments used to experimentally induce and inhibit LTD are indicated in green and red, respectively. Figure used with permission, copyright (2007), National Academy of Sciences, U.S.A. (Wong et al., 2007). (See Color Plate 8.1 in color plate section.)

LTD-like changes in synaptic plasticity, involving NR2B-subunit containing NMDARs and AMPAR endocytosis, underlie the effects of acute stress on spatial memory retrieval (Fig. 1; Yang et al., 2005; Wang et al., 2006; Fox et al., 2007; Wong et al., 2007).

Understanding the detailed mechanisms of how corticosterone release following acute stress alters glutamate transmission and subsequent synaptic plasticity and behavior requires further investigation. While it is possible that these effects are mediated by the classic actions of corticosterone on gene expression, the time course of the effects make this unlikely. For example, in the experiments of de Quervain et al. (1998) and Wong et al. (2007), the disruptive effects of acute stress on memory retrieval were observed 30 min after the initiation of the stressor. A number of recent studies suggest that corticosteroids have rapid, likely non-genomic actions on glutamate transmission in the central nervous system that may be mediated by unidentified membrane-associated receptors (Di et al., 2003; Karst et al., 2005; Tasker et al., 2006). Thus, non-genomic effects of stress hormones may at least partially explain the effects of acute stress on synaptic plasticity and spatial memory retrieval. However, as previously discussed, such an explanation is complicated by data showing that glucocorticoid receptor antagonists reverse the effects of

acute stress on synaptic plasticity (Xu et al., 1998) and increased corticosterone release is insufficient to disrupt memory retrieval (Woodson et al., 2003).

The results of these studies have important implications for theories of hippocampal-dependent learning and memory. In the case of spatial learning and memory, it is tempting to speculate that during the learning phase of a task such as the water maze, a memory for the platform location is formed by the potentiation of a subset of synapses in the hippocampus (Diamond et al., 2004). The activation of these synapses during subsequent retrieval allows the successful retrieval of the memory. As previously discussed, if acute stress is experienced immediately before retrieval, the memory is impaired (de Quervain et al., 1998; Wong et al., 2007). Given the points discussed above, it is possible that exposure to stress disrupted retrieval by saturating LTP in the hippocampus (Diamond et al., 2004, 2005). However, the recent results showing that specifically blocking the expression of LTD with the Tat-GluR2<sub>3Y</sub> peptide is sufficient to block the disruptive effects of stress on spatial memory retrieval refutes this hypothesis (Wong et al., 2007). Given that hippocampal CA1 LTD can be produced in an input specific manner, it is plausible that stress could depress only those synapses that were potentiated in the original learning episode. Alternatively, stress may “reset” the entire

hippocampal network by depressing all synapses, whether or not they were potentiated during learning (Diamond et al., 2005). Finally, as previously discussed, acute stress may affect hippocampal metaplasticity and thereby alter the optimal balance of LTP and LTD within the hippocampal circuit for memory retrieval (Kim and Yoon, 1998; Huang et al., 2005). Although a number of possibilities remain regarding the exact mechanism that allows stress to disrupt spatial memory retrieval, it is clear that altered patterns of synaptic plasticity which specifically favor the induction of LTD in the hippocampus ultimately underlies these behavioral effects.

## Conclusion

This review focused on recent research aimed at understanding the role of hippocampal synaptic plasticity in learning and memory. In the context of acute stress, we provided strong support for the hypothesis that distinct forms of synaptic plasticity underlie the effects of experience on learning and memory. In particular, recent results from our laboratory and others suggest that stress-enabled hippocampal LTD underlies the deficits in spatial memory retrieval commonly observed after acute stress (Wang et al., 2006; Fox et al., 2007; Wong et al., 2007). The conclusions drawn from these experiments were made possible by using two recently developed specific inhibitors for LTD. However, specific inhibitors of LTP are still lacking. Thus, efforts aimed at the development of additional compounds suitable for selectively inhibiting various forms of synaptic plasticity will be highly profitable for understanding the specific roles of synaptic plasticity in learning and memory.

## Abbreviations

AMPA	$\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor
CT	carboxyl tail
HIV	human immunodeficiency virus
HPA	hypothalamic–pituitary–adrenal

LTD	long-term depression
LTP	long-term potentiation
NMDAR	N-methyl-D-aspartate receptor

## Acknowledgments

John G. Howland is supported by fellowships from the Canadian Institutes of Health Research (CIHR) and the Michael Smith Foundation for Health Research (MSFHR). Yu Tian Wang is a Howard Hughes Medical Institute International Scholar, CIHR Investigator, MSFHR Senior Scholar, and Heart and Stroke Foundation of British Columbia and the Yukon Chair in Stroke Research.

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