



# Long-term potentiation at CA3–CA1 hippocampal synapses with special emphasis on aging, disease, and stress

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Synaptic plasticity in the mammalian central nervous system has been the subject of intense investigation for the past four decades. Long-term potentiation (LTP), a major reflection of synaptic plasticity, is an activity-driven long-lasting increase in the efficacy of excitatory synaptic transmission following the delivery of a brief, high-frequency train of electrical stimulation. LTP is regarded as a principal candidate for the cellular mechanisms involved in learning and offers an attractive hypothesis of how memories are constructed. There are a number of exceptional full-length reviews published on LTP; the current review intends to present an overview of the research findings regarding hippocampal LTP with special emphasis on aging, diseases, and psychological insults.

**Keywords:** aging, brain, hippocampus, LTP, stress, Alzheimer's disease

## INTRODUCTION

Over the past 30 years, extensive research has provided an enormous amount of data on the characteristics underlying the cellular and molecular mechanisms of synaptic plasticity. The Polish psychologist, Konorski (1948), first introduced the term “synaptic plasticity” to describe persistent and activity-dependent changes in synaptic strength. Several forms of long-lasting synaptic plasticity have been observed in the mammalian central nervous system (CNS); long-term potentiation (LTP); and long-term depression (LTD) represent two major forms of neuronal plasticity. LTP is a long-lasting activity-dependent enhancement in excitatory synaptic strength following the delivery of a brief, high-frequency train of electrical stimulation, while LTD is long-lasting decrease in synaptic efficacy following a low-frequency stimulation. LTP, along with other forms of synaptic plasticity is generally considered the closest neural model for the cellular mechanism involved in learning and memory storage (Bliss and Collingridge, 1993; Abel et al., 1997; Malenka and Nicoll, 1999; Martin et al., 2000; Lynch, 2004; Malenka and Bear, 2004).

Originally, LTP was discovered at excitatory glutamatergic synapses between perforant path fibers originating from the entorhinal cortex and granule cells in the dentate gyrus of the hippocampus of a rabbit *in vivo* (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). Subsequently, LTP has been investigated in a variety of mammalian species utilizing *in vitro* approaches including rat (Douglas and Goddard, 1975), mouse (Nosten-Bertrand et al., 1996), guinea pig (Harris and Cotman, 1986), monkey (Urban et al., 1996), and human (Chen et al., 1996; Beck et al., 2000; Cordoba-Montoya et al., 2010). Since its initial demonstration in the hippocampus (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973; Douglas and Goddard, 1975), LTP has been observed in various brain regions throughout the mammalian CNS, including the amygdala (Clugnet

and LeDoux, 1990; Rogan et al., 1997; Sigurdsson et al., 2007), cortex (Artola and Singer, 1987; Teyler, 1989; Jung et al., 1990; Tsumoto, 1990; Kirkwood et al., 1993; Fox, 2002), striatum (Calabresi et al., 1992; Charpier and Deniau, 1997; Lovinger, 2010), ventral tegmental area (Nugent et al., 2007, 2008), cerebellum (Salin et al., 1996; Lev-Ram et al., 2002), and nucleus accumbens (Pennartz et al., 1993; Kombian and Malenka, 1994; Schotanus and Chergui, 2008). LTP can be observed both *in vitro* as well as *in vivo* condition.

The pioneering work of Bliss and Lomo (1973) encouraged numerous investigators to pursue research in understanding the attributes of LTP. The relevance and great amount of interest within the neuroscience community in researching LTP can be easily established by performing a simple search on PubMed; there were hardly 30 publications just after the discovery of LTP (1973–1980) but currently, there are over 8000 research articles published on the topic and this list is growing every day. Although it has been almost 40 years since the discovery of LTP, it is still a remarkably attractive research topic and a paragon of immense importance to all of us who are involved in understanding its clandestine nature. Many outstanding full-length review articles have been published on LTP (Bliss and Collingridge, 1993; Bear and Malenka, 1994; Malenka, 1994, 2003; Collingridge and Bliss, 1995; Malenka and Nicoll, 1999; Sanes and Lichtman, 1999; Malenka and Bear, 2004; Cooke and Bliss, 2006; Joels and Krugers, 2007; Sigurdsson et al., 2007; Abraham and Williams, 2008; Blundon and Zakharenko, 2008; Kerchner and Nicoll, 2008; Sacktor, 2008; Feldman, 2009; Minichiello, 2009; O'Dell et al., 2010; Vogt and Canepari, 2010; Baudry et al., 2011). This current article intends to present a brief summary of the research findings on LTP in the hippocampus, including induction, characteristics, cellular mechanisms, and modulation with special emphasis on aging, pathological conditions, and stress.

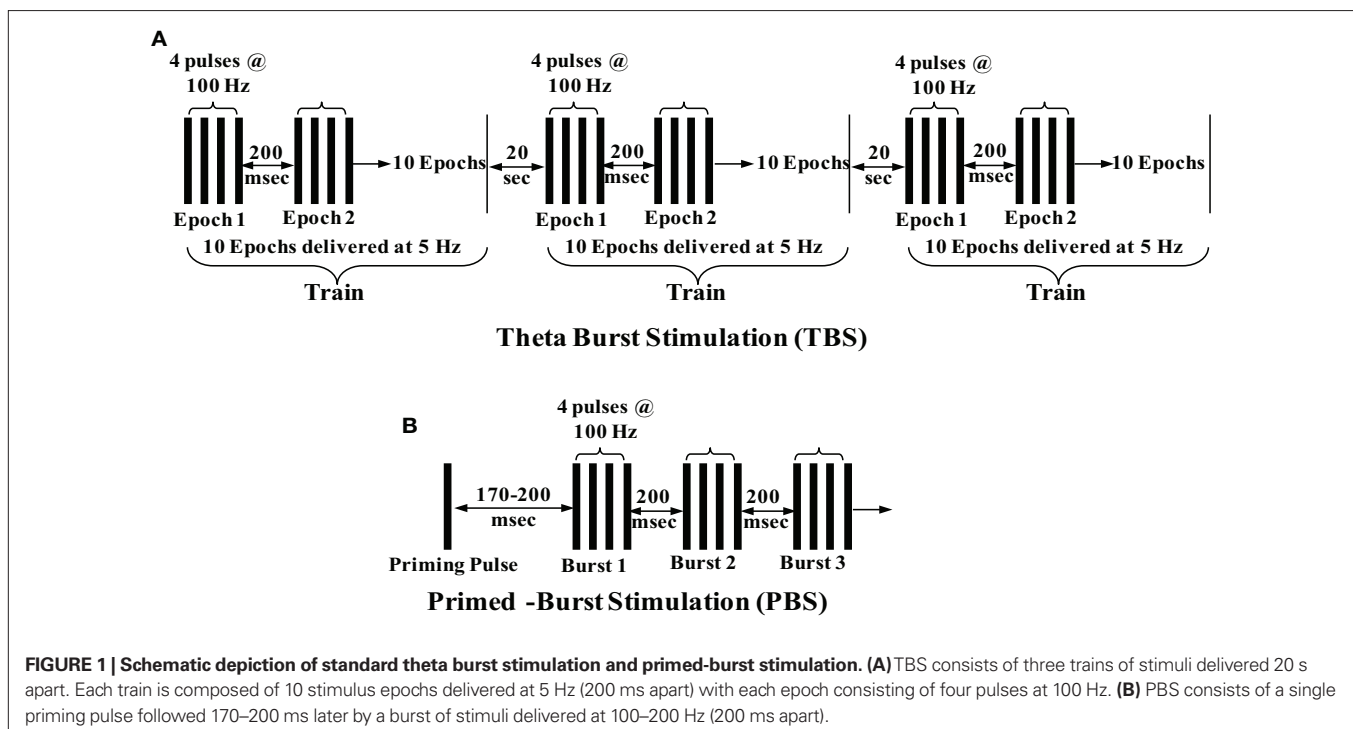
## INDUCTION PROTOCOLS

Since the pioneering discovery of LTP induction via a brief burst of high-frequency (100 Hz) electrical stimulation, various physiological stimulation paradigms have been employed to induce LTP. Because 100 Hz is not a rate at which neurons normally fire, the pursuit of more physiological naturally occurring firing patterns led to the discovery of several stimulation protocols. Under natural conditions, when a mouse or rat is exploring, hippocampal pyramidal neurons fire action potentials at a frequency of about 5 Hz, resulting in what is known as “theta rhythm,” a sinusoidal oscillation of the hippocampal electroencephalography, which is critical for mnemonic processing (Bland, 1986). This frequency led investigators to develop theta burst stimulation (TBS) and primed-burst stimulation (PBS) protocols (Larson and Lynch, 1986; Rose and Dunwiddie, 1986). TBS consists of three trains of stimuli delivered 20 s apart. Each train is composed of 10 stimulus epochs delivered at 5 Hz (200 ms apart) with each epoch consisting of four pulses at 100 Hz (Figure 1A). PBS includes a single priming pulse followed 170–200 ms later by a burst of stimuli delivered at 100–200 Hz, 200 ms apart (Figure 1B). Various modifications have been made to these protocols in many different studies. Although less physiological, another stimulation protocol used to elicit LTP is a 200-Hz stimulation (Grover and Teyler, 1990). Thus, brief and high-frequency stimulation protocols are usually employed to induce LTP, but there are several studies that have reported induction of LTP by low-frequency stimulation (Mayford et al., 1995; Thomas et al., 1996; Lante et al., 2006; Huang and Kandel, 2007; Habib and Dringenberg, 2009, 2010). For example, O’Dell’s lab demonstrated LTP induction by single pulse at 5 or 10 Hz stimulation (900 pulses; Mayford et al., 1995; Thomas et al., 1996), and other studies have established LTP following prolonged 1 Hz stimulation

(Li et al., 1998; Lante et al., 2006; Huang and Kandel, 2007; Habib and Dringenberg, 2009, 2010). Our work also demonstrates induction of LTP following low-frequency stimulation (5 Hz, 900 pulses) under a blockade of  $Ca^{2+}$  release from intracellular stores (ICS) during senescence (Kumar and Foster, 2004). However, the low-frequency stimulation paradigm is not usually used to induce LTP, and more research is needed to clearly delineate the mechanisms that contribute to this type of LTP and learn how they may differ from those underlying high frequency-induced LTP.

## TYPES AND PHASES OF LTP

Different areas of the brain exhibit different forms of LTP, which further depend on a number of factors including age of the organism and stimulation protocol. Depending upon the reliance of LTP on the *N*-methyl-D-aspartate (NMDA) receptor, two major types of LTP, NMDA receptor-dependent, and NMDA receptor-independent, have been identified (Grover and Teyler, 1992; Cavus and Teyler, 1996). For example, LTP induced at the CA3–CA1 hippocampal synapses employing high-frequency stimulation or TBS is dependent on the NMDA receptor (Collingridge et al., 1983; Harris et al., 1984; Morris et al., 1986), while an NMDA-independent form of LTP can be induced at the same synapse by using either a 200-Hz stimulation protocol (Grover and Teyler, 1990; Grover, 1998), tetraethylammonium application (Powell et al., 1994), or activation of metabotropic G-protein coupled receptors (Bashir et al., 1993; Bortolotto and Collingridge, 1993; Bortolotto et al., 1999; Fernandez de Sevilla et al., 2008; Anwyl, 2009; Fernandez de Sevilla and Buno, 2010). LTP at mossy fiber-CA3 synapses is sustained by NMDA receptors (Rebola et al., 2008). Another example of NMDA-independent LTP is that which is induced by high-frequency stimulation at the mossy fiber pathway in the hippocampus (Harris and



Cotman, 1986). To avoid ambiguity, this review will focus on the NMDA receptor-dependent form of LTP at Schaffer-collateral/commissural synapses in area CA1 of rat and mouse hippocampus.

Long-term potentiation is a multiphasic phenomenon and current models divide LTP into at least three different phases: an initial LTP (I-LTP), early LTP (E-LTP), and late LTP (L-LTP; Frey et al., 1993; Roberson et al., 1996; Sweatt, 1999), although an intermediate phase of LTP has also been suggested (Winder et al., 1998). I-LTP, also referred to as short-term potentiation, represents the foremost stage of LTP and is a continual form of NMDA receptor-dependent synaptic plasticity. I-LTP lasts about 30–60 min and does not require protein kinase activity (Roberson et al., 1996). E-LTP, which is evoked by fewer tetanic stimuli and lasts 2–3 h, is also independent of protein kinase activity (Frey et al., 1993). L-LTP, induced by delivery of multiple tetanic stimuli, lasts 5–6 h and requires protein synthesis and gene expression (Frey et al., 1993). For more details regarding phases of LTP, readers are recommended to consult two recently published books (Sweatt, 2003; Andersen et al., 2007).

### PROPERTIES OF NMDA RECEPTOR-DEPENDENT LTP

Long-term potentiation at the Schaffer-collateral pathway exhibits several basic characteristics which make it an attractive neural candidate for the storage of information; these include the principles of associativity, cooperativity, input-specificity, and persistence. The associativity principle indicates that a weak tetanic stimulation, activating few fibers, is insufficient for the induction of LTP. However, simultaneous strong stimulation of a neighboring pathway will trigger LTP at both synaptic pathways (Levy and Steward, 1979). Cooperativity occurs when a weak stimulation is paired with a strong postsynaptic depolarization. In this case, LTP will occur only when depolarization of postsynaptic cell occurs within about 100 ms of transmitter release from the presynaptic cell. Input-specificity stipulates that LTP will occur only in synapses which received tetanic stimulation, but inactive synapses that contact the same neuron will not share synaptic enhancement (Andersen et al., 1977; Lynch et al., 1977). Thus, these properties entail the conditional requirements needed for information storage. Finally, regarding persistence, LTP can last for several hours in the *in vitro* slice preparation and for many months in the freely moving animals (*in vivo*; Abraham, 2003), suggesting an ability for sustained physiological change consistent with memory formation.

### CELLULAR/MOLECULAR MECHANISMS INVOLVED IN LTP

Coincidence detection and temporal integration, two major aspects of dendritic integration, depend critically on the spatial and temporal properties of the dendritic summation of synaptic inputs (Magee, 2000; Segev and London, 2000). Changes in neuronal activity capable of inducing LTP lead to enhanced linearity of the spatial summation of synchronous excitatory postsynaptic potentials. Neuronal activity is likely to regulate dendritic integration of synaptic inputs. Bidirectional changes in the summation of excitatory postsynaptic potentials accompanying synaptic plasticity (LTP/LTD) are induced by correlated presynaptic and postsynaptic activity; induction of LTP at CA3–CA1 hippocampal synapses leads to persistent augmentation of dendritic summation of two Schaffer-collateral inputs and summation occurs only at the potentiated input (Wang et al., 2003; Xu et al., 2006).

Multiple molecular and cellular mechanisms throughout the CNS contribute to induction, expression, and maintenance of LTP. An array of amino acid receptors including the NMDA receptor are involved in the induction of LTP. Induction of E-LTP occurs when the intracellular concentration of  $\text{Ca}^{2+}$  inside the postsynaptic cell exceeds a critical threshold. The transient influx of  $\text{Ca}^{2+}$  into the cell requires the NMDA receptors, which are ionotropic non-selective cationic glutamate receptors that play a central role in the rapid regulation of synaptic plasticity. Activation of NMDA receptors requires binding of a ligand (glutamate), membrane depolarization to remove the  $\text{Mg}^{2+}$  block of the channel, and binding of a co-agonist (glycine). Thus, these receptors behave like a molecular coincidence detector by allowing ionic flux only when the above conditions are met. Since the NMDA receptor is a non-selective cation channel, its activation and opening leads to simultaneous influx of  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ions (Chen et al., 2005), although they are the predominant ionotropic glutamate receptor subtype most permeable to  $\text{Ca}^{2+}$  ions (Jahr and Stevens, 1993; Garaschuk et al., 1996).

A tetanic stimulation of presynaptic fibers causes release of neurotransmitters, mainly glutamate, onto the postsynaptic cell membrane. The binding of glutamate to postsynaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors triggers the influx of positively charged sodium ions into the postsynaptic cell and causes the cell to depolarize. The magnitude of depolarization determines the amount of  $\text{Ca}^{2+}$  entry into the postsynaptic cell. If the degree of depolarization is sufficient to remove the  $\text{Mg}^{2+}$  block of the NMDA receptor, then the channel will allow influx of  $\text{Ca}^{2+}$  into the cell.  $\text{Ca}^{2+}$  signal is necessary for the induction of LTP, which determines the degree and duration of LTP. The rapid rise in intracellular  $\text{Ca}^{2+}$  concentration triggers the activation of several enzymes, specifically kinases, such as calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC), that mediate induction of E-LTP (Sweatt, 1999). CaMKII is a multi-subunit (10–12) enzyme and each of the subunits has a catalytic domain and an autophosphorylation domain. Activation of CaMKII by  $\text{Ca}^{2+}$  and calmodulin can autophosphorylate the enzyme, which will remain active independent of the continued presence of  $\text{Ca}^{2+}$  (Lisman, 1994). PKC has a regulatory domain and a catalytic domain and can be activated by a variety of second messengers including  $\text{Ca}^{2+}$ , diacylglycerol, arachidonic acid, and other phospholipids (Nishizuka, 1992). Activation of PKC in response to a rise in  $\text{Ca}^{2+}$  is transient, but PKC can be phosphorylated in an autonomous manner without the continued presence of  $\text{Ca}^{2+}$  (Inoue et al., 1977). CaMKII and PKCs play an important role in induction of E-LTP, and their ability to autophosphorylate, independent of second messengers, plays an essential role in maintenance of E-LTP (Klann et al., 1993; Sacktor et al., 1993; Lisman, 1994; Sacktor, 2008).

Late LTP is the natural extension of E-LTP and represents the final phase of LTP. The hallmark of L-LTP is the requirement of gene transcription and its dependence upon protein synthesis (Frey et al., 1988; Frey and Morris, 1997; Kelleher et al., 2004). A transient rise in  $\text{Ca}^{2+}$  concentration, due to influx through NMDA receptors, stimulates  $\text{Ca}^{2+}$ -sensitive adenylyl cyclase enzymes, which catalyze production of 3',5'-cyclic adenosine monophosphate (cAMP; Chetkovich et al., 1991; Chetkovich and Sweatt, 1993; Frey et al., 1993; Xia and Storm, 2005). The rise in cAMP activates another

group of protein kinases, including protein kinase A (PKA; Huang et al., 1996). The phosphorylated PKA can activate mitogen-activated protein kinases, specifically extracellular regulated kinase (ERK). Once activated, ERK phosphorylates transcription factors, such as cAMP-response element-binding protein (CREB). Results suggest that transducers of regulated CREB (TORC), which are potent regulators of CREB activity, play a pivotal role in molecular mechanisms involved in L-LTP (Kovacs et al., 2007). The phosphorylated CREB activates the cAMP-response element, which induces changes in gene transcription and triggers synthesis of new proteins (Impey et al., 1996; Sweatt, 1999), many of which are yet to be determined. Downstream regulatory element antagonist modulator (DREAM) protein, calsenilin, has been recently suggested to be involved in LTP at perforant path-dentate gyrus molecular layer synapses; an impairment in LTP has been observed in calsenilin knockout mice (Lilliehook et al., 2003). However, a recent study demonstrated that LTD but not LTP was impaired in DREAM knockout mice at the hippocampal CA1 region (Wu et al., 2010).

The basic question as to whether the mechanisms underlying LTP, both the causes and locus of expression, result from changes in presynaptic or postsynaptic function remains contentious, for more details see Bekkers and Stevens (1990), Kullmann and Nicoll (1992), Isaac et al. (1995), Liao et al. (1995), Bolshakov et al. (1997), Debanne et al. (1997), Routtenberg (1999), Zakharenko et al. (2001), Emptage et al. (2003), Martin and Buno (2003), Nicoll (2003), Huang et al. (2005), Bayazitov et al. (2007), Lauri et al. (2007), Fernandez de Sevilla et al. (2008), Kerchner and Nicoll (2008), and Cabezas and Buno (2011). For more details about molecular-cellular mechanisms of LTP, readers are referred to several informative reviews published over the course of three decades (Madison and Schuman, 1991; Bliss and Collingridge, 1993; Malenka, 1994, 2003; Roberson et al., 1996; Nicoll and Malenka, 1999; Sanes and Lichtman, 1999; Sweatt, 1999; Brecht and Nicoll, 2003; Malenka and Bear, 2004; Shi et al., 2005; Miyamoto, 2006; Kerchner and Nicoll, 2008; Minichiello, 2009; Li et al., 2010a; Baudry et al., 2011; Kelly et al., 2011a).

### THE ROLE OF $Ca^{2+}$ IN INDUCTION OF LTP

As stated previously, LTP can be induced by a wide variety of stimulation paradigms, and in all cases, induction of LTP requires a substantial rise in intracellular  $Ca^{2+}$ . Thus, a  $Ca^{2+}$  signal is necessary for the induction of LTP and its regulation plays a significant role in determining the degree and duration of LTP. The major sources of intracellular  $Ca^{2+}$  include  $Ca^{2+}$  influx through ligand-gated glutamate receptors, such as NMDA receptors or various voltage-dependent  $Ca^{2+}$  channels (VDCCs), as well as the release of  $Ca^{2+}$  from ICS (Ghosh et al., 1994; Geiger et al., 1995; Berridge, 1998; Kumar and Foster, 2004).

It is generally accepted that at CA1 hippocampal synapses, NMDA receptors provide the foremost source of  $Ca^{2+}$  for LTP induction following stimulation frequencies near the threshold for synaptic modification (Johnston et al., 1992; Cavus and Teyler, 1996). However, the level of  $Ca^{2+}$  in dendritic spines can be influenced by VDCCs, ICS, and other glutamate receptors (Jaffe et al., 1994; Christie et al., 1996, 1997; Dingleline et al., 1999; Korkotian and Segal, 1999). Interestingly, several studies have shown that VDCCs and ICS are involved in regulating the threshold for induction of

synaptic modification (Foster and Norris, 1997; Norris et al., 1998; Wilsch et al., 1998; Rose and Konnerth, 2001; Foster and Kumar, 2002; Raymond and Redman, 2002; Kamsler and Segal, 2003; Kumar and Foster, 2004). Readers are referred to many excellent previously published articles for more details about the role of  $Ca^{2+}$  in LTP (Foster and Kumar, 2002; Atkins et al., 2005; MacDonald et al., 2006; Miyamoto, 2006; Tonkikh et al., 2006; Foster, 2007; Kumar et al., 2009; Simons et al., 2009; Barnes et al., 2010; Burke and Barnes, 2010; Diez-Guerra, 2010; Yoshioka et al., 2010; Munoz et al., 2011).

### REGULATION/NEUROMODULATION OF LTP

Neuromodulators, such as norepinephrine, serotonin, dopamine, acetylcholine, and histamine affect the induction of LTP and control the endurance of synaptic facilitation at Schaffer-collateral synapses. The hippocampus is densely innervated with noradrenergic (Cooper et al., 2003), cholinergic (Lewis et al., 1967; Amaral and Kurz, 1985; Frotscher and Leranthe, 1985; Gaykema et al., 1990), dopaminergic (Gasbarri et al., 1994a,b; Goldsmith and Joyce, 1994), serotonergic (Storm-Mathisen and Guldborg, 1974; Azmitia and Segal, 1978), and histaminergic (Panula et al., 1989) nerve terminals from the locus coeruleus, the medial septum–diagonal band complex, the substantia nigra–ventral tegmental area, dorsal–medial raphe nuclei, and tuberomammillary nucleus of the posterior hypothalamus, respectively. The endogenous release of neurotransmitters or agents acting on the receptors of these transmitter systems has the potential to regulate the induction of LTP. Readers interested in more details of the roles of various neurotransmitters in modulating LTP are advised to consult several previously published articles (Williams and Johnston, 1988; Blitzler et al., 1990; Staubli and Otaky, 1994; Brown et al., 1995; Otmakhova and Lisman, 1996; Wang and Arvanov, 1998; Costenla et al., 1999, 2010; Leung et al., 2003; Li et al., 2003; Tachibana et al., 2004; Doralp and Leung, 2008; Rebola et al., 2008; Buchanan et al., 2010; Fernandez de Sevilla and Buno, 2010; Luo and Leung, 2010; O'Dell et al., 2010; Swant et al., 2010).

Long-term potentiation can be modulated by a range of other agents, including corticosteroids (Foy et al., 1987; Diamond et al., 1989; Pavlides et al., 1993; McEwen, 1994; Sabeti et al., 2007; Maggio and Segal, 2010), caffeine (Lee et al., 1987; Lu et al., 1999a; Martin and Buno, 2003; Sajikumar et al., 2009; Alhaider et al., 2010; Costenla et al., 2010; Maggio and Segal, 2010), estrogen (Foy et al., 1999, 2001, 2008a,c), endocannabinoids (Terranova et al., 1995; Misner and Sullivan, 1999; Carlson et al., 2002; Chevaleyre and Castillo, 2004; Slanina et al., 2005; Chevaleyre et al., 2006, 2007; Abush and Akirav, 2010), flavonoids (Wang et al., 2011), inhibitors of histone deacetyltransferase activity (Alarcon et al., 2004; Haettig et al., 2011), neurotrophic factors (Kang and Schuman, 1995; Gottschalk et al., 1998; Korte et al., 1998; Xu et al., 2000; Kovalchuk et al., 2002; Fontinha et al., 2008; Sallert et al., 2009; Xie et al., 2010), nitric oxide/carbon monoxide (Bohme et al., 1991; Bon et al., 1992; Izumi et al., 1992, 2008; Zhuo et al., 1993, 1994, 1999; O'Dell et al., 1994; Arancio et al., 1996; Lu et al., 1999b; Taqatqeh et al., 2009; Carlini et al., 2010), purines (Wieraszko and Ehrlich, 1994; Costenla et al., 1999, 2010; Yamazaki et al., 2003; Fujii, 2004; Rebola et al., 2008; Maggi et al., 2009; Dias et al., 2011), orexin (Aou et al., 2003; Akbari et al., 2011), reducing agents (Tauck and

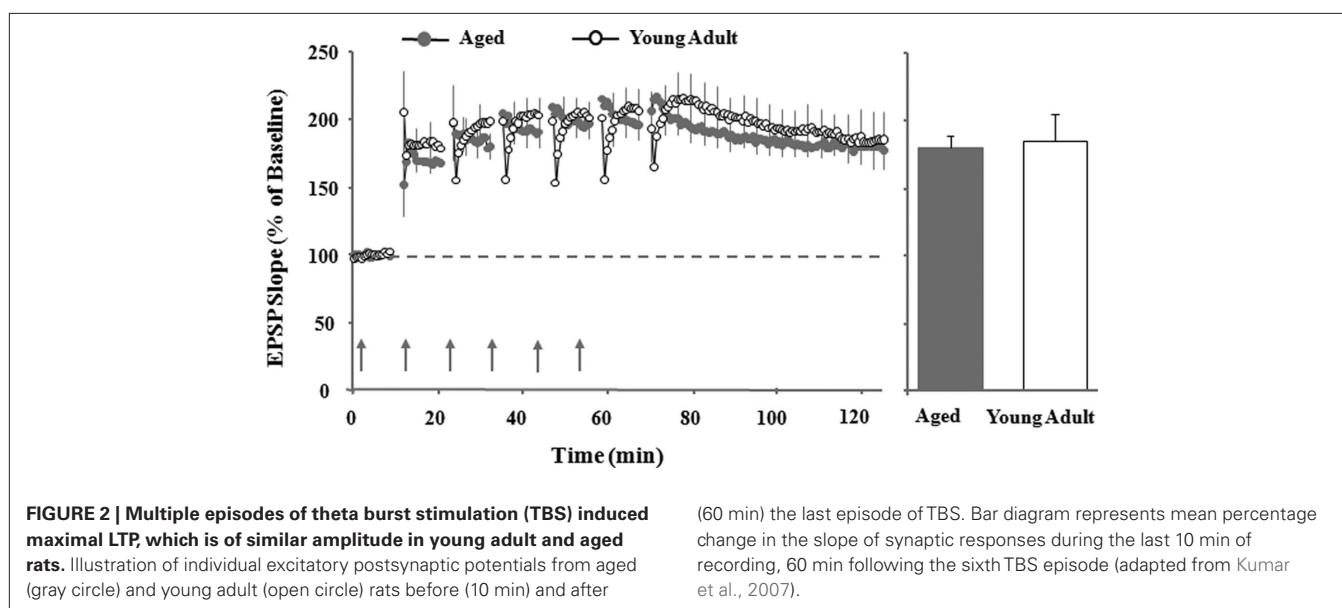
Ashbeck, 1990; Gozlan et al., 1995; Cai et al., 2008; Bodhinathan et al., 2010b; Cowley et al., 2011; Kelly et al., 2011b), and oxidizing agents (Watson et al., 2006). The presence of action potentials in the dendrites, which are mainly regulated by A-type potassium channels, can modulate induction of LTP (Magee and Johnston, 1997; Murphy et al., 1997; Johnston et al., 2000, 2003; Watanabe et al., 2002; Kim et al., 2007; Jung et al., 2011). Finally, metaplasticity, which refers to activity-dependent modulation of subsequent synaptic plasticity (Abraham and Bear, 1996; Abraham and Tate, 1997), can modulate LTP. In this case, previous activity/experience can influence the ability of hippocampal CA1 synapses to undergo subsequent synaptic facilitation, for details see Abraham and Bear (1996), Abraham and Tate (1997), Wang and Wagner (1999), Abraham et al. (2001), Jung et al. (2008), Sajikumar et al. (2009), Motanis and Maroun (2010), and Narayanan and Johnston (2010).

### LTP DURING AGING

Aging is associated with decline in cognitive function, including learning and memory. Hippocampal-dependent spatial and episodic memory tasks, such as recently acquired verbal recall, are significantly impaired as a result of aging (Hulicka and Rust, 1964; Bruning et al., 1975; Giambra and Arenberg, 1993; Head et al., 2008; Lister and Barnes, 2009). Senescent physiology, including altered hippocampal synaptic plasticity, is thought to contribute to the decline in cognitive function associated with aging and age-associated neurodegenerative diseases (Barnes, 1979, 2003; Disterhoft et al., 1994; Lynch, 1998a; Rosenzweig and Barnes, 2003; Tombaugh et al., 2005; Disterhoft and Oh, 2006; Foster and Kumar, 2007; Lister and Barnes, 2009). In general, no age-related differences are observed in the magnitude of LTP (Landfield et al., 1978; Barnes, 1979; Deupree et al., 1993; Moore et al., 1993; Diana et al., 1994a; Norris et al., 1996; Shankar et al., 1998), however, aging is associated with a shift in synaptic plasticity favoring decreased synaptic transmission and a reduced ability to induce LTP (Landfield and Lynch, 1977; Landfield et al., 1978; Barnes, 1979, 1990, 1994; de Toledo-Morrell and Morrell, 1985; Davis et al., 1993; Deupree

et al., 1993; Moore et al., 1993; Lynch and Voss, 1994; Auerbach and Segal, 1997; Lynch, 1997, 1998a,b; McGahon et al., 1997; Murray and Lynch, 1998a,b; Shankar et al., 1998; Hsu et al., 2002; Watson et al., 2002, 2006; Blank et al., 2003; Rosenzweig and Barnes, 2003; Watabe and O'Dell, 2003; Griffin et al., 2006; Kelly et al., 2011b). It has been suggested that impairment of LTP may begin in middle age (Rex et al., 2005) and a shift in synaptic plasticity, favoring LTD over LTP, contributes to the decrease in synaptic transmission observed in aged animals (Foster, 1999). Aged, memory-impaired animals exhibit deficits in LTP induction, and altered hippocampal synaptic plasticity is one of the hallmarks of age-associated memory impairment in mammals (Foster, 1999; Tombaugh et al., 2002; Barnes, 2003; Rosenzweig and Barnes, 2003; Burke and Barnes, 2010). Results also suggest that aging is associated with an increase in LTP (Costenla et al., 1999).

In considering synaptic transmission during aging, it is important to note that the observed shift in synaptic modifiability is not due to a change in the expression mechanisms. For example, there is no age-related difference in the maximal LTP magnitude observed under conditions in which a strong burst of synaptic stimulation is delivered (Diana et al., 1994b; Norris et al., 1996; Shankar et al., 1998). In addition, significant LTP can be observed in aged animals when single pulses are combined with strong postsynaptic depolarization or weak stimulation is combined with increased  $Ca^{2+}$ ; our work, too, demonstrates that asymptotic LTP can be induced in aged animals by employing multiple episodes of TBS (Figure 2; Barnes et al., 1996; Watabe and O'Dell, 2003; Kumar et al., 2007). This suggests that signaling pathways for the induction of LTP are intact during senescence. In contrast, it has been shown that the threshold for LTP induction is increased in aged memory-impaired animals (Landfield et al., 1978; Deupree et al., 1993; Moore et al., 1993; Barnes et al., 1996; Norris et al., 1996; Foster and Kumar, 2007), due in part to impaired postsynaptic depolarization. Thus, during aging, there may be a shift in the mechanisms that regulate the induction (i.e., threshold) of synaptic plasticity rather than a loss of expression mechanisms (Kumar et al., 2007). This shift



**FIGURE 2 | Multiple episodes of theta burst stimulation (TBS) induced maximal LTP, which is of similar amplitude in young adult and aged rats.** Illustration of individual excitatory postsynaptic potentials from aged (gray circle) and young adult (open circle) rats before (10 min) and after

(60 min) the last episode of TBS. Bar diagram represents mean percentage change in the slope of synaptic responses during the last 10 min of recording, 60 min following the sixth TBS episode (adapted from Kumar et al., 2007).

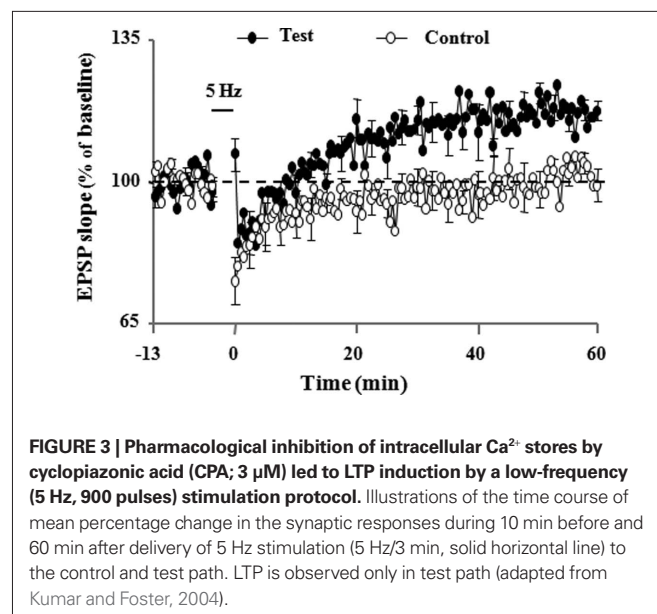
may favor synaptic weakening and could act as a functional lesion, reducing the ability for information to be transmitted through the hippocampus.

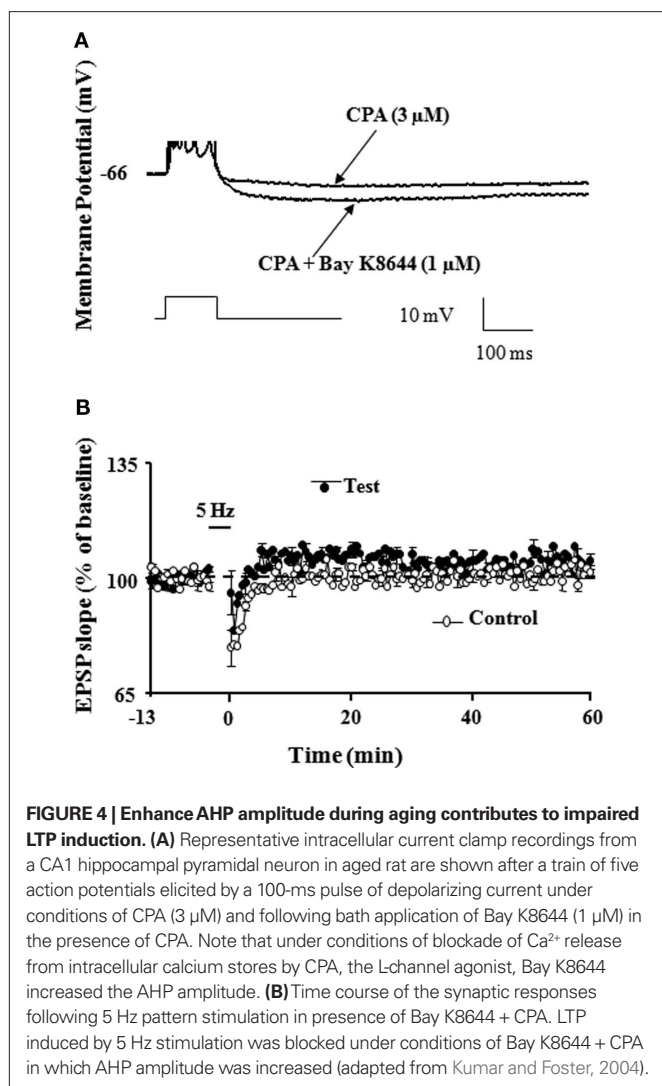
The NMDA receptor component of the synaptic response is decreased in aged animals (Barnes et al., 1997; Foster, 1999, 2007; Rosenzweig and Barnes, 2003; Billard and Rouaud, 2007; Bodhinathan et al., 2010b). Supporting this, several studies have shown that NMDA receptors contribute less  $\text{Ca}^{2+}$  to the induction of LTP in area CA1 of aged hippocampus when compared to the young hippocampus (Norris et al., 1998; Shankar et al., 1998; Boric et al., 2008). Changes in subunit expression, composition, and splice variants of NMDA receptors may also contribute to age-associated deficits of NMDA receptor function (Magnusson et al., 2002, 2005, 2006, 2010). However, there is a debate concerning whether NMDA receptor subunit expression actually decreases at hippocampal CA3–CA1 synapses (Foster, 2002). In addition, it is possible that functional differences result from posttranslational modifications associated with oxidation or phosphorylation states of the receptor (Foster, 2007).

Previous research examining the ability of reducing and oxidizing (redox) agents to modulate NMDA receptor activity in cell cultures and in tissue from neonates suggests that redox state is an important determinant of NMDA receptor function (Aizenman et al., 1989, 1990; Bernard et al., 1997; Choi and Lipton, 2000; Choi et al., 2001), possibly through oxidation of extracellular cysteine residues on the NMDA receptor (Lipton et al., 2002). Intracellular signaling molecules that affect NMDA receptor function are also sensitive to redox state. The aged brain exhibits an increase in oxidative damage (Harman, 1956; Beckman and Ames, 1998; O'Donnell et al., 2000; Kamsler and Segal, 2004; Serrano and Klann, 2004; Foster, 2006; Poon et al., 2006; Pieta Dias et al., 2007; Li et al., 2010b) and a decrease in redox buffering capacity (Parihar et al., 2008). Recently, our work demonstrated that the age-related decline in NMDA receptor-mediated synaptic responses is clearly related to the redox state associated with aging (Bodhinathan et al., 2010b). In addition, evidence has been provided that NMDA receptor function may be compromised due to altered  $\text{Ca}^{2+}$  homeostasis leading to increased activity of the  $\text{Ca}^{2+}$ -dependent phosphatase, calcineurin. Calcineurin activity depends on a modest rise in intracellular  $\text{Ca}^{2+}$ , and aged memory-impaired animals exhibit an increase in calcineurin activity (Foster et al., 2001). In turn, calcineurin can act on NMDA receptors to reduce  $\text{Ca}^{2+}$  influx (Lieberman and Mody, 1994; Tong and Jahr, 1994).

The idea that induction of LTP is subdued as a result of a reduction in NMDA receptor activation during aging is supported by research showing that induction deficits can be overcome by strong postsynaptic depolarization (Barnes et al., 1996). Indeed, there are several reasons to believe that an inability to achieve sufficient postsynaptic depolarization, a prerequisite for NMDA receptor activation, may be more problematic for LTP induction during senescence. First, the reduced synaptic strength of aged animals may result in a reduced afferent cooperativity in depolarizing the postsynaptic neuron and an inability to reach the level of depolarization needed for NMDA receptor activation. Moreover, it has been proposed that the inability to depolarize the cell is compounded during patterned stimulation, due to the larger after hyperpolarization (AHP). In fact, results suggest that it is the relatively large AHP which underlies

much of the LTP impairment found in these animals (Foster and Norris, 1997; Foster, 1999). Our work demonstrates that large AHP amplitude may mask the propensity of enhanced LTP induction during senescence (Kumar and Foster, 2004). Normally, there is a relationship between the frequency of afferent stimulation required for LTP induction and the level of resulting depolarization (Froemke et al., 2005), but during aging this is obscured by an increase in the  $\text{Ca}^{2+}$ -dependent,  $\text{K}^+$ -mediated AHP (Landfield and Pitler, 1984; Pitler and Landfield, 1990; Moyer et al., 1992; Disterhoft et al., 1996; Kumar and Foster, 2002; Tombaugh et al., 2005; Bodhinathan et al., 2010a). During aging, the large AHP may disrupt the integration of depolarizing postsynaptic potentials and the duration of this disruption has been proposed to be a function of the extent and duration of the AHP (Foster and Norris, 1997; Foster, 1999; Foster and Kumar, 2002). Hypothetically, the disruption would increase the level of stimulation needed for LTP, resulting in a plateau in the frequency-response function. In fact, our studies along with others, have demonstrated that the AHP amplitude is intimately involved in regulating the threshold for induction of LTP (Sah and Bekkers, 1996; Norris et al., 1998; Cohen et al., 1999; Sourdet et al., 2003; Kramar et al., 2004; Kumar and Foster, 2004; Le Ray et al., 2004; Murphy et al., 2004; Xu and Kang, 2005; Fuenzalida et al., 2007). Further, other evidence shows that pharmacological manipulations that reduce the AHP amplitude also shift the frequency-response functions, such that LTP can be observed following stimulation frequencies that would normally not elicit LTP. For example, pharmacological blockade of L-type  $\text{Ca}^{2+}$  channels, inhibition of  $\text{Ca}^{2+}$  release from ICS, or attenuation of  $\text{K}^+$  channels enables the induction of LTP following a modest stimulation in aged animals (Figure 3; Norris et al., 1998; Kumar and Foster, 2004). Similarly, our work also demonstrates that LTP can be inhibited by enhancement in the amplitude of the AHP following treatment with the L-channel agonist, Bay K8644 (Figure 4; Kumar and Foster, 2004). Although L-channel activity should provide more  $\text{Ca}^{2+}$ , the induction of LTP is impaired due to L-channel-induced enhancement in the AHP





amplitude. Thus, it is interesting to note that, while induction of LTP depends on a large rise in intracellular  $Ca^{2+}$ , LTP induction is facilitated by blocking several  $Ca^{2+}$  sources that contribute to the AHP during senescence.

Another method for investigating the relationship between the AHP and LTP threshold is to reduce the AHP amplitude through manipulation of the potassium channels. For example, blockade of SK-type potassium channels by apamin increases cell excitability and facilitates induction of LTP (Norris et al., 1998). Moreover, deletion of the  $Kv\beta 1.1$  subunit results in enhanced cell repolarization during repetitive firing by preventing A-type potassium channel inactivation. In turn, the normal spike broadening and increased  $Ca^{2+}$  influx through VGCCs is impaired by rapid repolarization. It follows then, that in  $Kv\beta 1.1$  knockout mice, the AHP is reduced and LTP is facilitated (Murphy et al., 2004). These results indicate that the source of  $Ca^{2+}$  provides an overriding control of synaptic modifiability, shifting the threshold frequency for LTP induction.

NMDA receptor activation following high-frequency stimulation leads to a robust rise in  $Ca^{2+}$ ; this rise in  $Ca^{2+}$  activates  $Ca^{2+}$ -dependent protein kinases that phosphorylate proteins, such as the

GluR1 subunit of the AMPA receptor, which mediates the expression of LTP. In contrast, a modest rise in  $Ca^{2+}$  results in synaptic depression through activation of protein phosphatases that dephosphorylate AMPA receptors, for review, see Xia and Storm (2005). Thus, due to the differential level of  $Ca^{2+}$  involved in the generation of various forms of synaptic plasticity, any treatment that modifies  $Ca^{2+}$  influx to the cytoplasm can influence the direction and degree of synaptic plasticity. The dependence on intracellular  $Ca^{2+}$  levels in determining the specific form of synaptic plasticity coincides with the observation that stimulation patterns for the induction of LTP and synaptic depression tend to require high- and low-frequency patterns, respectively.

Theoretical models suggest that synaptic plasticity is a function of synaptic activity, such that low-frequency stimulation induces synaptic depression. As neural activity increases, there is a transition from net LTD to induction of LTP (Bienenstock et al., 1982; Artola and Singer, 1993). A basic assumption of these models is that the threshold frequency for synaptic modification can “slide,” or is modifiable. Thus, changes in synaptic plasticity thresholds can be identified by plotting the change in synaptic strength as a result of different conditioning stimulation frequencies. This is referred to as the frequency-response function. The thresholds for induction of depression and LTP, as defined by afferent activity, are thought to reflect activity-dependent changes in the level of intracellular  $Ca^{2+}$ , which in turn activates  $Ca^{2+}$ -dependent enzymes.

Aging is associated with altered regulation of  $Ca^{2+}$  homeostasis (Landfield and Pitler, 1984; Gibson and Peterson, 1987; Khachaturian, 1989; Thibault et al., 1998, 2007; Mattson et al., 2000; Foster and Kumar, 2002; Toescu et al., 2004; Disterhoft and Oh, 2006; Foster, 2006, 2007; Mattson, 2007; Toescu and Verkhatsky, 2007; Kumar et al., 2009). The shift in  $Ca^{2+}$  homeostasis, increased amplitude of AHP, and altered  $Ca^{2+}$  signaling involving an alteration in the activity of phosphatases and kinases also give rise to increased susceptibility to induction of synaptic depression during senescence. In aged animals, blockade of NMDA receptors can reduce, but does not necessarily prevent, synaptic depression (Norris et al., 1998). These results indicate a shift in  $Ca^{2+}$  homeostasis such that aging cells exhibit reduced  $Ca^{2+}$  influx from NMDA receptors and an increased contribution from VGCCs and ICS during neural activity (Foster, 1999). In addition, it is likely that aged neurons exhibit changes in intracellular buffering and processes for extrusion of  $Ca^{2+}$ . Collectively, this shift results in alterations in physiology, including an increase in the AHP amplitude and impaired LTP induction, at least under physiological  $Ca^{2+}/Mg^{2+}$  conditions.

The change in  $Ca^{2+}$  homeostasis, which shifts the cell away from  $Ca^{2+}$  influx through NMDA receptors may be neuroprotective against  $Ca^{2+}$  mediated damage and thus act as compensation for increased vulnerability to neurotoxicity (Phillips et al., 1999). Alternatively, the shift in  $Ca^{2+}$  homeostasis could result from age-related increase in oxidative stress (Squier, 2001; Annunziato et al., 2003; Serrano and Klann, 2004). Reactive oxygen species could induce a rise in intracellular  $Ca^{2+}$  through release of  $Ca^{2+}$  from  $Ca^{2+}$ -binding proteins (i.e., decreased buffering) and oxidation of  $Ca^{2+}$  regulatory proteins (such as calmodulin) would disrupt ICS and increase entry through  $Ca^{2+}$  channels (Suzuki et al., 1997; Squier, 2001). In the hippocampus, oxidative stress has effects that mimic aging by increasing  $Ca^{2+}$  influx through L-channels (Lu et al., 2002;

Akaishi et al., 2004), increasing the function of Ca<sup>2+</sup>-dependent K<sup>+</sup> channels (Gong et al., 2000, 2002) and decreasing NMDA receptor function (Lu et al., 2001). Furthermore, oxygen radicals can influence the activity of Ca<sup>2+</sup>-dependent enzymes. The unstable super oxide (O<sup>•-</sup>) or high levels of H<sub>2</sub>O<sub>2</sub> (beyond the physiological range) inhibit calcineurin in tissue homogenates (Kamsler and Segal, 2003, 2004; Ullrich et al., 2003). However, in intact tissue, reactive oxygen species increase calcineurin activity, either through changes in the calcineurin inhibitory protein (Lin et al., 2003) or altered Ca<sup>2+</sup> regulation involving increased Ca<sup>2+</sup> from ICS and VGCCs, leading to impaired induction of LTP (Kamsler and Segal, 2004). Results from a series of studies by Marina Lynch's group elegantly demonstrated the role of oxygen free radicals and anti-oxidants in sustaining impaired LTP induced by age and stress associated neuroinflammation (Nolan et al., 2005; Griffin et al., 2006; Lynch et al., 2007a; Clarke et al., 2008; Loane et al., 2009; Cowley et al., 2011; Kelly et al., 2011b); for reviews see Lynch (2010). Future research will be required in order to determine whether treatments designed to reduce oxidative stress can reverse age-associated impaired LTP. The role of Ca<sup>2+</sup> regulation has been a major focus of research for age-related impairment in LTP and for more details readers are advised to consult the following review articles: (Disterhoft et al., 1994; Khachaturian, 1994; Landfield, 1994; Muller et al., 1996; Foster and Norris, 1997; Thibault et al., 1998, 2007; Verkhatsky and Toescu, 1998; Foster, 1999, 2006, 2007; Foster and Kumar, 2002; Toescu et al., 2004; Toescu and Verkhatsky, 2007; Kumar et al., 2009). Also, as suggested above, age-induced impairment in neuromodulation may contribute to the progression of senescent physiology, including impaired LTP and decline in cognitive function; for reviews see Potier et al. (1993), Disterhoft et al. (1999), Wu et al. (2002), Disterhoft and Matthew Oh (2003), Mesulam (2004), Backman et al. (2006), Billard (2006), Canas et al. (2009), Duzel et al. (2010), and Niewiadomska et al. (2009).

Aging is associated with an increased activation of microglia and astrocytes (Lynch et al., 2007a; Lyons et al., 2007), which may contribute to impaired LTP associated with senescence (Griffin et al., 2006; Lynch, 2010). Results are emerging which support that antagonists (minocycline, atorvastatin, rosiglitazone, or the polyunsaturated fatty acid, eicosapentaenoic acid), that inhibit glial activation, are capable of sustaining LTP in animals where it is normally compromised (Nolan et al., 2005; Griffin et al., 2006; Lynch et al., 2007a; Clarke et al., 2008; Loane et al., 2009; Cowley et al., 2011; Kelly et al., 2011b). Future studies are required to determine the role of microglia in LTP and underlying mechanisms.

## LTP DURING STRESS

Stress, from mild anxiety to mental trauma, perilously disturbs biological, physiological, and psychological dynamic equilibrium; acute as well as chronic stress has a profound influence on brain-body interaction and considerably contributes to cognitive deficits (Foy et al., 1987; McEwen and Sapolsky, 1995; Kim et al., 1996; Kim and Yoon, 1998; McEwen, 1999, 2008; Kim and Diamond, 2002; Artola, 2008; van Stegeren, 2009; Wolf, 2009; Maggio and Segal, 2010; Rothman and Mattson, 2010; Foy, 2011). A stimulus that has the ability to induce stress causes release of corticosterone from the adrenal glands. Corticosterone acts on the corticosterone receptors, mineralocorticoid (MR) and glucocorticoid (GR), which are distributed throughout

the body including the hippocampus (Reul and de Kloet, 1985; Patel et al., 2000), and produce an appropriate response to manage the stressful event. The classical view of the influence of stress on LTP and memory functions presumes an inverted U-shape curve, such that a low-mild stress level facilitates but a high level impairs LTP induction (Diamond et al., 1992; Joels, 2006); however, the inverted U-shape effect of stress on LTP is not fully explained by this model (Maggio and Segal, 2010). The discovery of membrane-bound corticosterone receptors, mMR and mGR, which act through novel non-genomic pathways, can affect ionic conductances and modify cell excitability and function (Karst et al., 2005; Karst and Joels, 2005; de Kloet et al., 2008; van Gemert et al., 2009), in addition to two classical genomic nuclear corticosterone receptors, the MR and GR, which contribute to slow and persistent change in the function of cell (de Kloet et al., 1999; Joels, 2001), further complicates the influence of stress on LTP. Results from a recent study demonstrate that persistently augmented hippocampal corticotropin-releasing hormone and its interaction with corticotropin-releasing hormone receptor type 1, which reside on dendrites of CA1 pyramidal cells, contributes to impairment in LTP and cognitive function associated with chronic early life stress (Ivy et al., 2010).

Long-term potentiation at the hippocampal synapses is virtually abolished following acute or chronic stress (Foy et al., 1987, 2008b; Shors et al., 1989; Xu et al., 1997; Pavlides et al., 2002; Alfarez et al., 2003; Diamond et al., 2005; Artola et al., 2006; Kavushansky et al., 2006; Foy, 2011). However, LTP can still be induced during stress by employing higher effective postsynaptic depolarization (Artola et al., 2006). Further, depending upon the brain area, stress influences LTP differently. For example, chronic psychological stress impairs LTP induction in hippocampal area CA1, while it has no effect on dentate gyrus LTP (Gerges et al., 2001). Similarly, acute stress or physiological concentrations of corticosterone can inhibit induction of LTP in dorsal hippocampus while LTP is facilitated in the ventral hippocampus (Maggio and Segal, 2007, 2011). In addition, corticosterone facilitates VDCC-dependent LTP while NMDA-dependent LTP is impaired in the CA1 area of the hippocampus (Krugers et al., 2005; Maggio and Segal, 2007). Stress evoked by opiate withdrawal facilitates LTP (Dong et al., 2006). The concentration of cGMP depends on the rates of synthesis by soluble guanylyl cyclase and degradation by phosphodiesterase (PDE). PDEs are implicated in modulation of LTP (Barad et al., 1998; Kuenzi et al., 2003; Navakkode et al., 2004). Results from a recent study suggest that enhanced cAMP-specific PDE4 activity contributes to impaired LTP associated with acute stress (Chen et al., 2010a). The effects of stress (behavior, acute, chronic, fear, escape, traumatic brain injury) on LTP in the hippocampus are well documented (Foy et al., 1987, 2008b; Shors et al., 1989, 1997; Diamond et al., 1994; Diamond and Rose, 1994; Garcia et al., 1997; Xu et al., 1997; Albensi et al., 2000; O'Donnell et al., 2000; Vereker et al., 2001; Alfarez et al., 2002, 2003; Pavlides et al., 2002; Gerges et al., 2004; Rocher et al., 2004; Hui et al., 2005; Li et al., 2005; Schwarzbach et al., 2006; Kim and Haller, 2007; Kohda et al., 2007; Artola, 2008; Ryan et al., 2008; Ivy et al., 2010; Kamal et al., 2010; Sterlemann et al., 2010; Tran et al., 2010; Maggio and Segal, 2011). Overall, results suggest that stress profoundly influences the induction of LTP; intensity of stress (mild, acute, chronic) and area of the hippocampus (CA1, DG, ventral or dorsal hippocampus) play



critical roles in determining the degree and direction of stress-induced alteration in the LTP. Future studies will resolve the role of specific receptor types and signaling mechanisms contributing to stress-induced alterations in synaptic potentiation.

In general, aging and stress both negatively influence induction of LTP; there are several commonalities between advanced age and stress, including enhanced neuroinflammation and oxidative stress, which could contribute to impaired LTP in both circumstances (Lynch, 1998a; Murray and Lynch, 1998a,b; Foy et al., 2008b; Sterlemann et al., 2010). Results are emerging, which suggest that proteins, such as kinases, which are activated by stress, are also involved in LTP impairment associated with aging; O'Donnell et al. (2000) eloquently demonstrated that the activity of two stress-induced mitogen-activated protein kinases, c-Jun NH<sub>2</sub>-terminal kinase (JNK) and p38 are increased with advanced age which could contribute to impairment in LTP induction during senescence. Future studies are required to determine the impact of stress and aging interaction on LTP and underlying signaling cascades.

### LTP DURING PATHOLOGICAL CONDITIONS

Like aging, various neurodegenerative diseases and pathological conditions influence induction of LTP and determine the degree and duration of synaptic strength. Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly population; the hippocampus is especially susceptible in AD and early degenerative symptoms include substantial deficits in the performance of hippocampal-dependent cognitive abilities such as spatial learning and memory. The cognitive impairments observed in AD patients are widely believed to be due to the progressive disruption of synaptic function and neurodegeneration triggered by aggregated amyloid- $\beta$ , which is implicated in the pathogenesis of AD and contributes to the impairment of LTP (Cullen et al., 1997; Freir and Herron, 2003; Costello and Herron, 2004; Klyubin et al., 2004; Wang et al., 2004a,b; Costello et al., 2005; Welsby et al., 2007; Schmid et al., 2008, 2009; Shankar et al., 2008; Shipton et al., 2011). Results demonstrate that amyloid- $\beta$  specifically interacts with several major intracellular signaling pathways including the Ca<sup>2+</sup>-dependent protein phosphatase calcineurin, CaMKII, cAMP/PKA, protein phosphatase 1, and CREB, all of which are downstream of NMDA receptor signaling and alter hippocampal LTP (Zhao et al., 2004; Knobloch et al., 2007; Wang et al., 2009; Yamin, 2009; Zeng et al., 2010). One study recently demonstrated that amyloid- $\beta$ -induced impairment in LTP results from perturbed CaMKII signaling pathways but could be rescued by pretreatment with brain-derived neurotrophic factors (Zeng et al., 2010). Other results suggest that amyloid- $\beta$  closely interacts with and attenuates synaptic AMPA receptors contributing to impairments in LTP (Parameshwaran et al., 2007). Changes in LTP have been observed in several animal models of AD (Chapman et al., 1999; Jacobsen et al., 2006; Abbas et al., 2009; Auffret et al., 2009, 2010; Gengler et al., 2010; Middei et al., 2010; Ondrejcek et al., 2010; Tran et al., 2010). Review of literature suggests that a deficit in LTP induction is associated with AD and there is increasing evidence which suggests that impaired LTP is an event occurring early in AD pathology.

In addition to protein kinase, calcium-dependent lipases may contribute to the molecular mechanisms implicated in LTP by modulating AMPA receptors (Okada et al., 1989; Massicotte et al.,

1990, 1991; Gagne et al., 1996). Apolipoprotein E (ApoE) is synthesized predominantly by the astrocytes in the brain and plays a critical role in regulation of plasma cholesterol and participates in transport of dietary lipids (Mahley et al., 1984; Mahley, 1988); ApoE comprises three isoforms, apoE2, apoE3, and apoE4 and has been reported in the general human population with apoE4 being the most common isoform, which is genetically associated with late onset of the AD (Schmechel et al., 1993). ApoE could play a role in synaptic plasticity through lipid homeostasis. Altered cellular metabolism of ApoE knockouts contributes to the neuropathology and cognitive deficits that develop in AD. In some studies, LTP is impaired in apoE-deficient mice (Masliah et al., 1996, 1997; Krugers et al., 1997), but another study reported no significant change in LTP (Anderson et al., 1998); furthermore, one study found a significant impairment in LTP only in young but not in aged ApoE knockout mice (Valastro et al., 2001). Results demonstrate that modulation of AMPA receptor could be a possible mechanism involved in impaired LTP observed in ApoE knockouts (Valastro et al., 2001). For further readings, see Trommer et al. (2004, 2005), Yun et al. (2007), Korwek et al. (2009), Chen et al. (2010b), and Dumanis et al. (2011).

In addition to AD, an impairment in LTP induction has been observed in several other pathological conditions, including diabetes (Biessels et al., 1996; Kamal et al., 1999, 2000, 2005; Valastro et al., 2002; Artola et al., 2005; Artola, 2008), Parkinson's disease (Bageetta et al., 2010), Fragile X Syndrome (Lauterborn et al., 2007; Connor et al., 2011), Down syndrome (Costa and Grybko, 2005; Siarey et al., 2005), Rett syndrome (Moretti et al., 2006; Weng et al., 2011), Huntington's disease (Usdin et al., 1999; Murphy et al., 2000; Lynch et al., 2007b), Niemann-Pick disease type C (Zhou et al., 2011), Rubinstein-Taybi syndrome (Alarcon et al., 2004), brain inflammation (Min et al., 2009; Lynch, 2010), glioma (Wang et al., 2010), and chronic liver failure (Monfort et al., 2007). Also, an impaired LTP has been observed following sleep deprivation (Campbell et al., 2002; Davis et al., 2003; McDermott et al., 2003; Kim et al., 2005; Ravassard et al., 2009; Aleisa et al., 2010; Alhaider et al., 2010, 2011; Poe et al., 2010; Xie et al., 2010), ethanol drinking (Randall et al., 1995; Schummers et al., 1997; Chandler, 2003; Wright et al., 2003; Stephens et al., 2005; Tokuda et al., 2007), lead exposure (Gilbert and Mack, 1998; Zhao et al., 1999), and thyroid deficiency (Dong et al., 2005; Sui et al., 2005). A review of the literature clearly demonstrates that neurodegenerative diseases, along with other pathological conditions, negatively impact induction, expression, and maintenance of LTP. However, in order to develop a therapeutic intervention to ameliorate impaired LTP, future studies should be designed to delineate the neural circuits, cellular mechanisms, and signaling pathways altered by diseases.

### CONCLUSION

Copious amounts of data generated over the past 38 years have provided insight regarding the complexities of the neural basis of learning and memory. Currently, LTP in the hippocampus is the vanguard and the best documented neuronal substrate for memory formation. A wealth of information relating the molecular and cellular signaling mechanisms underlying LTP induction, expression, and maintenance, has provided a ray of hope in delineating the ways

by which learning occurs and memories are formed. However, a full understanding of how memories are constructed and which neural circuits are responsible for acquisition, consolidation, and recall of created memories has not been accomplished. Aging, diseases, stress, and other pathological conditions adversely influence learning and memory capabilities. A plethora of information gathered over the last couple of decades demonstrates an impairment in LTP during aging, stress, and disease and is thought to contribute to a decline in learning and memory performance. However, much work is needed in order to acquire a true understanding of LTP impairment resulting from various pathological conditions. Further progress in delineating the neural and cellular bases of

impaired LTP during aging, stress, and diseases and the impact on cognitive function will require an approach that emphasizes the importance of how neural pathways and signaling mechanisms are altered.

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