Shift in Induction Mechanisms Underlies an Age-Dependent Increase in DHPG-Induced Synaptic Depression at CA3–CA1 Synapses

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Kumar A, Foster TC. Shift in induction mechanisms underlies an age-dependent increase in DHPG-induced synaptic depression at CA3–CA1 synapses. J Neurophysiol 98: 2729–2736, 2007. First published September 26, 2007; doi:10.1152/jn.00514.2007. Several forms of log-term synaptic plasticity have been identified and the mechanisms for induction and expression of synaptic modifications change over development and maturation. The present study examines age-related changes in the induction of group I metabotropic receptor selective agonist (R,S)-3,5-dihydroxyphenylglycine (DHPG) induced long-term synaptic depression (DHPG-LTD) at CA3–CA1 synapses. The results demonstrate that the magnitude of DHPG-LTD is enhanced in male aged Fischer 344 rats compared with young adults. The role of mGluR1 in the induction of DHPG-LTD was increased with advanced age and, in contrast to young adults, induction involved a significant contribution of NMDA receptors and L-type Ca\(^{2+}\) channels. Moreover, the protein tyrosine phosphatase inhibitor sodium orthovanadate significantly attenuated DHPG-LTD only in young adults. The expression of DHPG-LTD in aged animals was dependent on protein synthesis and the enhanced expression was associated with an increase in paired-pulse facilitation. The results provide evidence that DHPG-LTD is one of the few forms of synaptic plasticity that increases with advanced age and suggest that DHPG-LTD may contribute to age-related changes in hippocampal function.

INTRODUCTION

There is mounting support for developmental and maturational regulation of synaptic plasticity, including the induction of long-term synaptic plasticity (LTD). In the hippocampal CA1 region, several mechanisms for induction of LTD have been characterized in young animals. One form can be induced by low-frequency synaptic activity, which depends on the activation of N-methyl-d-aspartate (NMDA) receptors. Various other forms of LTD have been identified that do not require NMDA-receptor activation. In these cases, induction depends on activation of other Ca\(^{2+}\) sources, voltage-gated L-type Ca\(^{2+}\) channels (Normann et al. 2000; Norris et al. 1998b; Wickens and Abraham 1991), intracellular Ca\(^{2+}\) stores (Kumar and Foster 2005), activation of metabotropic glutamate receptors (mGluRs) (Nicolle et al. 1998; Oliet et al. 1997; Palmer et al. 1997), or insulin (Huang et al. 2004).

The ability to induce mGluR-dependent LTD declines during development (Kemp et al. 2000; Nosyreva and Huber 2005; Overstreet et al. 1997). In contrast, advanced age is associated with an increased susceptibility to LTD induced by pattern synaptic activity (Foster and Kumar 2007; Hsu et al. 2002; Kumar and Foster 2005; Norris et al. 1996, 1998a; Vouimba et al. 2000). It is unclear what role mGluR signaling plays in the induction of LTD in aged animals. Relatively few studies have investigated alterations in the characteristics of group I mGluR signaling during aging and the results from a handful of studies on hippocampal mGluR signaling during senescence are mixed. Binding to group I mGluRs has been reported to decrease in region CA1 of aged mice (Magnusson 1998). Conversely, another report examining specific mGluR subtypes indicated that the level of mGluR1 expression is augmented in the hippocampus of aged rats (Simonyi et al. 2005). Similarly, an early study demonstrated that trans-1-amino-cyclopentyl-1,3-dicarboxylate (ACPD) increased the production of inositol 1,4,5-triphosphate (IP3) in the hippocampus of aged memory-impaired rats (Parent et al. 1995), whereas another study found a decrease in ACPD-induced IP3 turnover in the hippocampus of aged rats with cognitive deficits (Nicolle et al. 1999). Part of the problem may be the use of ACPD, which is an agonist of group II/III mGluRs.

The current study was designed to investigate mGluR-LTD during aging using the specific group I mGluR agonist (R,S)-3,5-dihydroxyphenylglycine (DHPG). The results indicate that the magnitude of DHPG-induced LTD (DHPG-LTD) is increased with advanced age. In contrast to young adult animals, induction of DHPG-LTD in aged animals depends on activation of mGluR1 and involves NMDA receptors and L-type Ca\(^{2+}\) channels. Expression of DHPG-LTD in aged animals was associated with an increase in paired-pulse facilitation. Finally, protein tyrosine phosphatase inhibition attenuated the DHPG-LTD in young adult but not in senescent rats. The results indicate an increase in DHPG-LTD with advanced age and point to a shift in DHPG-LTD mechanisms.

METHODS

Animals

Procedures involving animal subjects were reviewed and approved by the Institutional Animal Care and Use Committee of University of Florida and were in accordance with guidelines established by the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Male Fischer 344 rats, young (5–8 mo) and aged (22–26 mo), were group housed (two per cage), maintained on a 12:12-h light schedule, and provided unrestricted access to food and water.

Hippocampal slice preparation and electrophysiology

Rats were anesthetized with halothane (Halocarbon Laboratories, River Edge, NJ) and swiftly decapitated. The brains were rapidly
removed and the hippocampi were dissected. Hippocampal slices (~400 μm) were cut parallel to the alvear fibers using a tissue chopper. The slices were incubated in a holding chamber (room temperature) containing artificial cerebrospinal fluid (ACSF; in mM): NaCl 124, KCl 2, KH₂PO₄ 1.25, MgSO₄ 2, CaCl₂ 2, NaHCO₃ 26, and glucose 10. At 30 min before recording, one to two slices were transferred to a submersion recording chamber (Harvard Apparatus, Boston, MA) and held between two nylon nets. The chamber was continuously perfused with oxygenated (95% O₂-5% CO₂) ACSF at a flow rate of 2–3 ml/min. The pH and temperature were maintained at 7.4 and 30 ± 0.5°C, respectively. The first set of studies examined age-differences in DHPG-LTD in intact slices; however, due to a possible DHPG-induced hyperexcitability in the CA3 pyramidal cells (Cuellar et al. 2005; Tan et al. 2003; Young et al. 2004), all subsequent studies were conducted with the CA3 region removed.

Extracellular field potentials from stratum radiatum of CA1 were recorded with glass micropipettes (4–6 MΩ) filled with recording medium (ACSF). A concentric bipolar stimulating electrode (outer pole: stainless steel; 200-μm diameter; inner pole: platinum/iridium, 25-μm diameter; FHC, Bowdoinham, ME) was positioned about 1 mm from the recording electrode localized in the middle of stratum radiatum. A single diphasic stimulus pulse of 100 μs was passed by a stimulator (SD9 Stimulator; Grass Instrument, West Warwick, RI) to the Schaffer collateral commissural pathway to evoke field potentials at 0.025 Hz. In an attempt to control for possible synaptic plasticity processes initiated by the level of postsynaptic activity, the excitatory postsynaptic potential (EPSP) was set to about 1 mV and a response baseline was collected for ≥20 min before experimental manipulations (drug application) and for 30–60 min after drug washout.

The signals were amplified, filtered between 1 Hz and 1 kHz, and stored on computer disk for off-line analysis. Two cursors were placed around the initial descending phase of the waveform and the maximum slope (mV/ms) of the EPSP was determined by a computer algorithm that found the maximum change across all sets of 20 consecutively recorded points (20-kHz sampling rate) between the two cursors. Changes in transmission properties induced by application of drug were calculated as the percentage change from the averaged baseline responses collected. For paired-pulse stimulation, the interpulse interval was 50 ms. The paired-pulse facilitation (PPF) ratio was calculated by dividing the slope of the second synaptic response by the slope of the first response. To determine the effects of DHPG on the PPF ratio, the PPF ratio for each response was normalized by the average ratio calculated for the baseline recording. For paired-pulse stimulation, the ratio was calculated by dividing the slope of the second synaptic response by the ratio of the first response by the slope of the first response. To determine the effects of DHPG on the PPF ratio, the PPF ratio for each response was normalized by the average ratio calculated for the baseline recording.

All drugs were bath applied by addition to the ACSF. (R,S)-3,5-Dihydroxyphenylglycine (DHPG), (R,S)-1-aminoindan-1,5-dicarboxylic acid (AIDA), (+)-2-methyl-4-carboxyphenylglycine (LY367385), 6-methyl-2-(phenylethynyl)-pyridine (MPEP), cycloheximide, and 2-amino-5-phosphonopentanoic acid (AP5) were obtained from Tocris Bioscience (Ellisville, MO). DHPG (100 μM), cycloheximide (60 μM), sodium orthovanadate (1 mM; Sigma–Aldrich), and AP5 (100 μM) were dissolved directly in ACSF. LY367385 (200 μM), MPEP (10 μM), and nifedipine (10 μM; RBI) were initially dissolved in a small amount of dimethyl sulfoxide (DMSO) and diluted further by ACSF to a final DMSO concentration of 0.01%. AIDA (200 μM) was dissolved in 1.1 equiv NaOH and diluted in ACSF. All antagonists were bath applied for ≥20–30 min before application of DHPG and DHPG application at 15, 30, and 60 min after cessation of DHPG application (filled circle, n = 5) and young adult (open circle, n = 8) rats. Each response was computed as a percentage of the mean baseline response collected during the 20 min just before DHPG application. Error bars represent SEs and alternate with each time point.

FIG. 1. Synaptic depression induced by selective group I metabotropic glutamate receptor (mGluR) agonist (R,S)-3,5-dihydroxyphenylglycine (DHPG) is increased in aged rats. A: time course of synaptic responses showing the 20-min baseline before DHPG (100 μM) application, a rapid decrease during application (solid line), and continued synaptic depression during a 60-min washout in intact slices (i.e., with CA3 region attached) from aged (filled circle, n = 5) and young adult (open circle, n = 8) rats. Each response was computed as a percentage of the mean baseline response collected during the 20 min just before DHPG application. Error bars represent SEs and alternate with each time point. B: time course of DHPG influences on synaptic responses in slices after removal of region CA3 for aged (filled circle, n = 5) and young adult (open circle, n = 10) rats. C: representative traces of excitatory postsynaptic potential (EPSP) responses for the time points indicated in B. D: summary of mean synaptic depression induced during DHPG application at 15, 30, and 60 min after cessation of DHPG application in aged (filled bar) and young adult (open bar) rats. Error bars represent SEs. Asterisk represents a significance difference relative to baseline. Pound sign represents a significant difference between the aged and young adult groups. Number above each bar indicates number of slices recorded for each group at each time point.
had no noticeable effect on baseline synaptic transmission (data not shown).

Student’s t-tests were used to determine whether DHPG-induced changes in the synaptic response or the PPF ratio were different from baseline. ANOVA was used to examine the interaction of age and drug treatment and follow-up ANOVAs were used to localize age differences. Post hoc comparisons of the effects of pharmacological treatment relative to the control condition on the level of DHPG-LTD were performed using the Fisher protected least-significant difference (PLSD) test with significance set at $P < 0.05$. Where stated, $n$ represents the number of slices used in each set of experiment.

**RESULTS**

**DHPG-LTD is enhanced in senescent rats**

Bath application of DHPG (100 $\mu$M) for 10 min resulted in a rapid decrease in synaptic responses, which recovered somewhat during washout, and began to stabilize about 15 min after the start of washout. Figure 1A shows that 1 h after washout of DHPG, the magnitude of synaptic depression was greater $[t(11) = 6.1, P < 0.0001]$ in age rats ($n = 5$) compared with slices from young adult animals ($n = 8$).

Previous studies indicate that mGluR activation in the hippocampal region CA3 can induce a hyperexcitability of CA3 pyramidal cells (Cuellar et al. 2005; Tan et al. 2003; Young et al. 2004). Therefore all subsequent studies were conducted with the CA3 region removed. Control responses of DHPG-LTD were obtained in slices from aged ($n = 17$) and young ($n = 10$) animals and were interleaved with studies examining pharmacological antagonists and the means + SE were used for comparison of pharmacological manipulations (Fig. 6). In addition, paired-pulse stimulation was used to examine possible presynaptic influences. Figure 1, B and C illustrates the mean amplitude of DHPG-LTD in a subset of slices (young adult, $n = 10$; aged, $n = 8$) that were recorded for 60 min after the onset of DHPG washout. Interestingly, the level of DHPG-LTD was considerably reduced in young adult and aged animals after removal of region CA3 compared with intact slices (Fig. 1, A and B); however, DHPG continued to depress synaptic responses to a greater degree in senescent animals. Examination of each time point confirmed a significant age effect at 15 min $[t(25) = 3.7, P < 0.001]$, 30 min $[t(25) = 3.4, P < 0.005]$, and 60 min $[t(16) = 2.2, P < 0.05]$ after DHPG washout (Fig. 1D).

Examination of the normalized PPF ratios indicated that DHPG increased the PPF ratio, particularly for aged animals. Thus the PPF ratio was increased above baseline at all time points examined for aged animals (Fig. 2). In the case of young adults, the PPF ratio was increased above baseline at 30 and 60 min after the start of washout. Finally, the increase in the PPF was greater in aged animals relative to younger animals $[t(16) = 2.2, P < 0.05]$ at the 60-min time point (Fig. 2D).

**Differential involvement of mGluR1 in induction of DHPG-LTD during aging**

To examine the mechanisms that may underlie the age-related increase in DHPG-LTD, we first examined receptor selectivity. DHPG is a group I mGluR selective agonist and preincubation with the group I mGluR selective antagonist, AIDA (200 $\mu$M), completely blocked the early and later phases of DHPG-LTD in aged animals (Fig. 3A). We further tested the...
role of group I mGluR subtypes in aged animals using the mGluR1 and mGluR5 selective antagonists LY367385 (200 μM) and MPEP (10 μM), respectively. LY367385 (n = 5) blocked the rapid synaptic depression normally observed after DHPG application and MPEP (n = 5) attenuated this early phase of DHPG-LTD (Fig. 3B). Moreover, both the mGluR1 and mGluR5 selective antagonists blocked the later depression such that the synaptic responses measured 30 min after the start of DHPG washout were not different from the baseline response in slices from aged animals (Fig. 3B).

Examination of mGluR1 and mGluR5 selective antagonists in slices from young adults revealed an age-dependent difference in their ability to block DHPG-LTD (Fig. 3C). Similar to the effect in aged animals, MPEP (n = 6) attenuated the early phase and blocked longer-term DHPG-LTD (100.66 ± 6.83%). In contrast, LY367385 (n = 5) attenuated only the early phase and DHPG-LTD (77.72 ± 3.33%) was observed 30 min after the start of DHPG washout (Fig. 3C). Thus an age difference was observed for the mGluR1 antagonist, which blocked the early and later phases of DHPG-LTD in aged rats and attenuated only the early phase in young adults.

Role of Ca^{2+} sources in DHPG-LTD in aged animals

Previous reports indicate that DHPG induced an enhancement of the NMDA receptor function (Doherty et al. 2000; Fitzjohn et al. 1996; Harris et al. 2003; Mannaioni et al. 2001) and increased Ca^{2+} influx through L-channels (Bonsi et al. 2005; Derjean et al. 2005; Endoh 2004; Heinke and Sandkuhler 2005; Kreitzer and Malenka 2005; Mao and Wang 2002, 2003). To determine whether these sources of Ca^{2+} contributed to the enhancement of DHPG-LTD in aged animals, NMDA receptors and L-channels were blocked with AP5 (100 μM) and nifedipine (10 μM), respectively, before application of DHPG. Figure 4A shows that in the presence of AP5, DHPG-LTD could be observed in slices from aged rats (n = 6); however, the NMDA receptor blocker significantly attenuated DHPG-LTD compared with control conditions (Fig. 6A). No effect of AP5 was observed for DHPG-LTD in young adult rats (n = 7) (Fig. 4B). Similarly, Fig. 4C shows that DHPG-LTD was induced in the presence of the nifedipine (n = 5); however, blockade of L-channels reduced the magnitude of DHPG-LTD in aged (Figs. 4C and 6A) but not in young adult (n = 5) animals (Figs. 4D and 7B).

Signaling cascades

The results indicate that the increase in DHPG-LTD in aged animals is due in part to activation of different induction mechanisms (e.g., mGluR1, NMDA receptors, and L-channels). Therefore we examined possible differences in the mGluR signaling cascades. In aged rats, preincubation (20–30 min) of slices with the protein synthesis inhibitor cycloheximide (60 μM, n = 5) blocked the DHPG-LTD (Fig. 5A). In agreement with previous studies in young adult rats (Huang and Hsu 2006; Moult et al. 2002, 2006) the protein tyrosine

![FIG. 3. DHPG-LTD in aged animals depends on activation of both mGluR1 and mGluR5 receptor subtypes. A: group I mGluR selective antagonist, (R,S)-1-aminoindan-1,5-dicarboxylic acid (AIDA, 200 μM) completely blocked DHPG-LTD in slices from aged animals (n = 2). B: in slices obtained from aged rats, (+)-2-methyl-4-carboxyphenylglycine (LY367385; filled circle, 200 μM, n = 5) blocked the early and later synaptic depression induced by DHPG, mGluR5 antagonist, 6-methyl-2-(phenylethynyl)-pyridine (MPEP; open diamond, 10 μM, n = 5), reduced the early phase (compare with control, open circle) and completely blocked the DHPG-LTD 30 min after washout. C: in slices from young adult rats, LY367385 (filled circle, n = 5) and MPEP (open diamond, n = 6) reduced the early phase (compare with control, open circle) and MPEP blocked the later DHPG-LTD.](http://jn.physiology.org/content/jn/98/5/2732/F3.large.jpg)
phosphatase inhibitor sodium orthovanadate blocked the DHPG-LTD in young adults (Fig. 5B). However, sodium orthovanadate failed to block the DHPG-LTD in slices obtained from senescent rats (68.49 ± 1.89, n = 5) (Fig. 5C).

Figure 6 provides a summary of the level of DHPG-LTD in aged and young adult rats for the same pharmacological manipulations. An ANOVA constructed on the magnitude of LTD indicated a significant interaction of age and treatment conditions \( F(5,69) = 5.22, P < 0.0005 \). Follow-up ANOVAs in each drug condition indicated that, in addition to the control condition, DHPG-LTD was greater in aged animals under conditions of blockade of tyrosine phosphatase \( F(1,8) = 85.2, P < 0.0001 \). In contrast, DHPG-LTD was greater in young adult animals under conditions of mGluR1 blockade \( F(1,8) = 12.9, P < 0.01 \). Planned comparisons of treatment effects relative to the level of LTD under control conditions were performed using Fisher’s PLSD with significance set at \( P < 0.05 \). Results indicated a reduction in the level of DHPG-LTD in the presence of the mGluR5 receptor antagonist MPEP and orthovanadate in young adult rats (Fig. 6B). For aged animals, differences relative to control were observed for mGluR-receptor antagonists MPEP and LY367385, the Ca\(^{2+}\)-channel blocker, nifedipine, and the NMDA-receptor blocker AP5 (Fig. 6A). Although AP5 reduced the level of depression, NMDA-receptor blockade did not completely block DHPG-LTD. Finally, ANOVAs within each age group, on the change in the PPF ratios after DHPG application, indicate no difference across pharmacological manipulations.

**DISCUSSION**

The present study demonstrates that DHPG-LTD is enhanced in aged animals relative to young adults. The age-related difference in DHPG-LTD involves an increased role for mGluR1. Previous work indicates variable contributions of mGluR1 and mGluR5 for DHPG-LTD in young animals. Several studies demonstrated that mGluR5 antagonists blocked DHPG-LTD, whereas blockade of mGluR1 receptors was less effective (Faas et al. 2002; Fitzjohn et al. 1999; Hou and Klann 2004). The current study confirms that blockade of mGluR5 with MPEP blocked DHPG-LTD in young adult animals, whereas LY367385 had little or no effect. In addition, we have extended these results, demonstrating that blockade of mGluR1 or mGluR5 was equally effective at preventing the induction of DHPG-LTD in aged animals. The ability of an mGluR1 antagonist to block DHPG-LTD in aged but not in young adults indicates increased mGluR1 participation in DHPG-LTD with advanced age.

Interestingly, the activation of either receptor can initiate similar signaling cascades (Berkeley and Levey 2003; Hou and Klann 2004; Volk et al. 2006), suggesting that the differential effects may be due to disparity in the level of receptors or differences in receptor location. The mGluR1-mediated decrease in synaptic responses is thought to involve a presynaptic reduction in transmitter release, which can be observed as an increase in the PPF ratio (Faas et al. 2002; Mannaioni et al. 2001; Tan et al. 2003). Presynaptic mGluR1 mechanisms are...
generally more apparent in neonates and more prominent in mediating the expression of the early phase of synaptic depression. Thus inhibition of mGluR1 blocks the early phase of DHPG-LTD in neonates (Mannaioni et al. 2001) and reduces the early phase only in young adults (Faas et al. 2002; Hou and Klann 2004). In the current study, this early phase was completely blocked by the mGluR1 antagonist in aged rats. Furthermore, enhanced DHPG-LTD was associated with an increase in the PPF ratio in aged animals, supporting the idea that age differences are due, at least in part, to increased mGluR1 function.

The density of group I mGluRs is highest on dendritic spines of CA1 pyramidal cells with the mGluR5 receptor exhibiting much greater expression than mGluR1 (Fotuhi et al. 1994; Lujan et al. 1996; Romano et al. 1995; Shigemoto et al. 1997). Interestingly, expression of mGluR1 in the hippocampus may decrease as immunoreactivity for mGluR5 increases over postnatal development (Lopez-Bendito et al. 2002). This shift in expression may contribute to the shift from presynaptic to postsynaptic mechanisms for expression of LTD over the course of synapse formation and maturation (Dumas and Foster 1997; Nosyreva and Huber 2005). In contrast, the level of mGluR1 expression is augmented in the hippocampus with advanced age (Simonyi et al. 2005), which is consistent with the increased influence of mGluR1 in mediating the induction of DHPG-LTD of aged animals in the present study. The fact

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**FIG. 5.** DHPG-LTD signaling cascades in aged animals. A: preincubation of slices obtained from aged animals with the protein synthesis inhibitor cycloheximide (60 μM) blocked the DHPG-LTD (n = 5). Preincubation with the protein phosphatase inhibitor orthovanadate (1 mM) blocked DHPG-LTD in slices from (B) young adult animals (n = 5) and (C) failed to block the DHPG-LTD in aged rats (n = 5). Solid line in each panel indicates the duration of DHPG (100 μM) application. Insets: representative traces of the EPSP responses before (1), during (2), and after (3) DHPG application for the indicated time points.

**FIG. 6.** Bar diagram showing effects of pharmacological treatments on the DHPG-LTD, measured 30 min after DHPG washout, for the 2 age groups. All antagonists were applied 20–30 min before DHPG application. A: in aged animals, DHPG-LTD was blocked (i.e., not different from baseline indicated by the dashed line) by preincubation of slices with LY367385 (LY36), MPEP, or nifedipine (Nife). Relative to the control (cont) condition, the level of DHPG-LTD was reduced by preincubation with LY36, MPEP, Nife, or AP-5. Relative to young adults (B), DHPG-LTD was greater in aged animals under control condition and during protein phosphatase inhibition by orthovanadate (Orth). In young adults, DHPG-LTD was blocked by MPEP and orthovanadate, such that the level of LTD was different from the control condition and not different from baseline. Furthermore, compared with aged, young adults exhibited greater DHPG-LTD under condition of mGluR1 blockade by LY367385. Asterisk (*) indicates significant depression from baseline (dashed line), pound sign (#) indicates significant difference from the control level of DHPG-LTD within each age group, and dagger symbol (†) indicates significantly larger DHPG-LTD between age groups.
that the PPF ratio was greater in aged animals, ≥60 min after washout, suggests that the enhanced DHPG-LTD in aged animals involves presynaptic mechanisms. However, an age difference in the PPF ratio was not observed for other time points, leaving open the possibility for an enhancement in postsynaptic mechanisms.

Several forms of chemically induced LTD have been defined by differences in induction mechanisms (e.g., NMDA-LTD, DHPG-LTD, insulin-LTD). Similarly, synaptic activity-dependendent LTD can be differentiated according to the involvement of different receptors or voltage-dependent channels. The enhanced LTD after application of DHPG in aged animals involves NMDA receptors and voltage-gated L-type Ca\(^{2+}\) channels, indicating involvement of more than one mechanism. DHPG can increase NMDA-receptor function (Doherty et al. 2000; Fitzjohn et al. 1996; Harris et al. 2003; Mannaioni et al. 2001) and mounting evidence indicates that DHPG increases Ca\(^{2+}\) influx through L-type channels (Bonsi et al. 2005; Derjean et al. 2005; Endoh 2004; Heinke and Sandkühler 2005; Kreitzer and Malenka 2005; Mao and Wang 2002, 2003). In the present study, the NMDA-receptor antagonist AP5 did not block DHPG-LTD in young adult or aged animals; however, the level of DHPG-LTD was reduced in aged animals compared with the control condition, indicating that NMDA-receptor activation contributes to the enhancement of DHPG-LTD in the older group. The involvement of NMDA receptors suggests that the age-related increase in synaptic depression may relate to the level of postsynaptic depolarization (Hu et al. 2005) or increased CA3–CA1 synaptic activity. Indeed, DHPG-LTD in young adult and aged animals was reduced by removal of region CA3. However, it is important to note that the age-related enhancement of DHPG-LTD was maintained in slices in which CA3 was removed, indicating that the age-related differences were not simply due to increased CA3 excitability. In contrast, mGluR1 activation depolarizes CA1 pyramidal cells (Mannaioni et al. 1999) such that an increase in mGluR1 function in aged animals could engage voltage-dependent mechanisms including NMDA receptors and voltage-gated L-channels.

Different forms of LTD may involve different signaling pathways and the involvement of various signaling pathways can shift over the course of development (Li et al. 2007; Nosyreva and Huber 2005; Wang et al. 2007). In the current study, the protein tyrosine phosphatase inhibitor sodium orthovanadate blocked DHPG-LTD only in young adult rats as previously reported (Huang and Hsu 2005; Moul et al. 2002, 2006) and failed to block DHPG-LTD in age rats, suggesting an age-dependent shift in signaling processes. Interestingly, application of insulin to hippocampal slices can induce LTD, which depends on L-channel activity and protein synthesis and is independent of the calcineurin-protein phosphatase 1 signaling cascade (Huang et al. 2004). Rather, insulin-induced LTD depends on tyrosine kinase signal transduction cascades and a similar cascade may be activated by both mGluR1 and mGluR5 (Hou and Klann 2004).

The level of NMDA-receptor-independent LTD induced by synaptic activity is consistently increased in aged animals (Foster and Kumar 2007). Further, research indicates an essential role for L-channels in LTD induced by synaptic activity (Norris et al. 1998). The results of the current study reveal that DHPG-LTD, similar to stimulation-induced LTD, is one of the few forms of synaptic plasticity that increases with advanced age (Foster 2002). As such, DHPG-LTD may contribute to an age-related reduction in synaptic transmission observed in aged and memory-impaired animals (Barnes et al. 2000; Deupree et al. 1993). However, the relationship between LTD and memory function is far from clear (Foster and Kumar 2007). Furthermore, mGluRs are involved in metaplasticity, regulating the threshold for synaptic modification (Bortolotto et al. 2005; van Dam et al. 2004). As such, mGluRs may have distinctive and time-dependent influences on the encoding (Manahan-Vaughan and Braunewell 2005) or consolidation (Maciejak et al. 2003) of memory. In either case, the finding of age-related differences in the mechanisms for induction of DHPG-LTD including a differential role of mGluR1, NMDA receptors, and L-channels provides an avenue for investigating the role of mGluRs in memory function during aging.

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