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Brief communication

# Repression of the eIF2α kinase PERK alleviates mGluR-LTD impairments in a mouse model of Alzheimer's disease

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ABSTRACT

Mounting evidence indicates that impairments of synaptic efficacy and/or plasticity may be a key step in the development of Alzheimer's disease (AD) pathophysiology. Among the 2 major forms of synaptic plasticity, long-term potentiation and long-term depression (LTD), much less is known about how LTD is regulated in AD and its molecular mechanisms. Recent studies indicate that metabotropic glutamate receptor 5 (mGluR5) may function as a receptor and/or co-receptor for amyloid beta. Herein, we examined mGluR-LTD in hippocampal slices from aged APP/PS1 mutant mice that model AD. Our findings demonstrate that mGluR-LTD is blocked in APP/PS1 mice, and that the mGluR-LTD failure is reversed by either genetically or pharmacologically suppressing the activity of PERK, a kinase for the mRNA translation factor eIF2α. These data are congruent with recent evidence that inhibition of eIF2α phosphorylation via PERK suppression and reversal of *de novo* protein synthesis deficits can mitigate cognitive deficits in neurodegenerative diseases. Together with reports indicating that mGluR5 may mediate amyloid beta synaptotoxicity, our findings offer insights into novel therapeutic targets for AD and other cognitive syndromes.



## 1. Introduction

Abundant evidence indicates that synaptic dysfunction that results in compromised synaptic efficacy and/or plasticity (the ability of synapses to strengthen or weaken over time) may be a key step during the development of Alzheimer's disease (AD) pathophysiology (Jacobsen et al., 2006; Ma and Klann, 2012; Ma et al., 2010; Oddo et al., 2003; Selkoe, 2002; Tomiyama et al., 2010). Thus, understanding the molecular signaling mechanisms underlying these synaptic impairments could yield insights into therapeutic targets for AD. Long-term potentiation (LTP) and long-term depression (LTD) are the intensely studied forms of synaptic plasticity that work in concert to mediate learning and memory as well as several other forms of experience-dependent changes in brain function (Malenka and Bear, 2004). LTP has been extensively studied in AD, either in the context of exogenous application of soluble beta-amyloid (Aβ), abnormal accumulation of which represents a brain pathology hallmark for AD, or in various transgenic mouse models of AD (Li et al., 2011; Ma and Klann, 2012; Rowan et al., 2005; Walsh et al., 2002). In contrast, very few studies have examined how the molecular mechanisms of LTD are altered in AD models. Moreover, to our knowledge, most of the previous LTD studies in AD have been conducted either in the context of acute exogenous Aβ application or relatively young (<1 year old), but not aged, transgenic mouse models of AD (D'Amelio et al., 2011; Kim et al., 2001; Li et al., 2009; Ma et al., 2012; Megill et al., 2015; Raymond et al., 2003; Wang et al., 2002).

There are two well-studied, mechanistically distinct forms of LTD: N-methyl-D-aspartate receptor (NMDAR)-dependent LTD and metabotropic glutamate receptor (mGluR)-dependent LTD. NMDAR-dependent LTD is usually induced by electrical low-frequency stimulation and requires activation of NMDARs, whereas mGluR-dependent LTD requires activation of group 1 mGluRs (includes mGluR1 and 5) and is often induced by (RS)-3,5-dihydroxyphenylglycine (DHPG), a selective agonist for group 1 mGluRs (Lüscher and Huber, 2010; Malenka and Bear, 2004).

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Of interest, recent studies indicate that mGluR5 may function as a receptor and/or co-receptor for Aβ, and an mGluR5 antagonist rescued cognitive defects in AD model mice (Hu et al., 2014; Um et al., 2013). However, the downstream signaling mechanisms mediating the previously described effects remain unclear.

Long-lasting forms of both LTP and LTD depend on intact mechanisms of *de novo* protein synthesis (Costa-Mattioli et al., 2009; Klann and Dever, 2004; Richter and Klann, 2009; Rosenberg et al., 2014). Protein synthesis is a highly regulated process, particularly at the initiation phase, and involves various translational factors including eukaryotic initiation factor 2 (eIF2), which plays a key role in synaptic plasticity and memory formation (Costa-Mattioli et al., 2007; Klann et al., 2004; Trinh and Klann, 2013). It is generally considered that in response to specific cellular stress, one (or more) of the four eIF2 kinases—PKR, HRI, GCN2, or PERK, is activated to phosphorylate eIF2 on the α subunit, leading to inhibition of general protein synthesis and potentially memory impairments if the decreases in protein synthesis are long-lasting (Ma and Klann, 2014; Trinh and Klann, 2013; Wek and Cavener, 2007; Wek et al., 2006). Notably, recent studies have suggested a link between neurodegenerative diseases, including prion disease and AD, and disruption of translational homeostasis due to abnormal PERK/eIF2α signaling. In particular, hyperphosphorylation of eIF2α via PERK activation is associated with AD and prion disease, and repression of PERK activity rescues cognitive deficits in mouse models of AD, prion disease, and frontotemporal dementia (Ma and Klann, 2014; Ma et al., 2013; Moreno et al., 2012, 2013; Radford et al., 2015).

Herein, we studied mGluR-LTD at CA3-CA1 synapses in hippocampal slices from aged APP/PS1 AD model mice. Our findings demonstrate that mGluR-LTD is blocked in AD mice, and importantly, the mGluR-LTD blockade is reversed by either genetically or pharmacologically suppressing activity of eIF2α kinase PERK. These data are congruent with evidence that inhibition of eIF2α phosphorylation via PERK suppression and consequently improved *de novo* protein synthesis can mitigate cognitive deficits in neurodegenerative diseases (Ma and Klann, 2014). Together with reports indicating that mGluR5 may mediate synaptotoxicity of Aβ (Hu et al., 2014; Um et al., 2013), our findings offer insights into novel therapeutic targets for AD and other cognitive syndromes.

## 2. Materials and methods

### 2.1. Mice

All mice were housed in a barrier facility dedicated to transgenic mice at Wake Forest University School of Medicine. The facility operates in accordance with standards and policies of the US Department of Agriculture's Animal Welfare Information Center and the NIH Guide for Care and Use of Laboratory Animals. The facility is kept on a 12 hours light and/or dark cycle, with a regular feeding and cage-cleaning schedule. Mice of either sex were used. APP/PS1 transgenic mice (APPswe + PSEN1/ΔE9) were purchased from the Jackson Laboratory (Jankowsky et al., 2001). PERK forebrain conditional knockout (PERK cKO) mice were generated as described previously (Trinh et al., 2012). Creation of APP/PS1/PERK cKO double mutant mice was done as described previously (Ma et al., 2013). All genotypes were verified by polymerase chain reaction. Mice were used at the age of 12–15 months, except for the exogenous Aβ application experiments, for which wild-type (WT) mice were used at the age of 3–6 months.

### 2.2. Hippocampal slices preparation and electrophysiology

Hippocampal slices were prepared as described previously (Ma et al., 2011). For electrophysiology experiments, slices were transferred to recording chambers (preheated to 32 °C) where they were superfused with oxygenated artificial cerebrospinal fluid. Monophasic, constant-current stimuli (100 μs) were delivered with a concentric bipolar microelectrode (FHC Inc, Bowdoin, ME, USA) placed in the stratum radiatum of area CA3, and the field excitatory postsynaptic potentials (fEPSPs) were recorded in the stratum radiatum of area CA1. fEPSPs were acquired, and amplitudes and maximum initial slopes measured, using pClamp 10 (Axon Instruments, Foster City, CA, USA). To induce mGluR-LTD, slices were perfused with DHPG (100 μM in artificial cerebrospinal fluid) for 10 minutes.

### 2.3. Drug treatment

DHPG (Abcam, Cambridge, MA, USA) was prepared as stock solution in distilled water and was diluted into a final concentration of 100 μM immediately preceding the experiments. Only DHPG stock prepared within 1 week was used in the experiments. PERK inhibitor I (GSK2606414, Calbiochem/Millipore) was prepared as stock solution in dimethyl sulfoxide and was diluted to its final concentration of 1 μM before conducting experiments. Aβ(1–42) stock (100 μM, Bachem) was prepared as described previously (Ma et al., 2010).

### 2.4. Western blot

As previously described (Ma et al., 2013), mouse hippocampal slices were flash frozen on dry ice after drug treatment, followed by standard procedure for Western blot. All primary and secondary antibodies were diluted in blocking buffer. Blots were probed with primary antibodies for phospho-eIF2α (1:1000; Cell Signaling), eIF2α (1:1000; Cell Signaling), PERK (1:1000; Santa Cruz), and GAPDH (1:10,000, Cell Signaling). Protein bands were visualized using chemiluminescence (Clarity ECL; Biorad) and the Biorad ChemiDoc MP Imaging System. Densitometric analysis was performed using Image Lab (Biorad).

### 2.5. Data analysis

Data are presented as mean ± standard error mean. Summary data are presented as group means with standard error bars. For comparison between two groups, a two-tailed independent Student's *t* test was used. For comparisons between multiple groups, analysis of variance was used followed by individual *post hoc* tests when applicable. Error probabilities of $p < 0.05$ were considered statistically significant.

## 3. Results

### 3.1. Hippocampal mGluR-LTD is impaired in APP/PS1 mice but unaltered with application of exogenous Aβ

We first asked whether mGluR-LTD was altered in AD model mice by using APP/PS1 mutant mice, a well-established AD model (Jankowsky et al., 2001). mGluR-LTD was induced at CA3-CA1 synapses (Schaffer collateral pathway) in hippocampal slices with application of group 1 mGluR agonist DHPG (100 μM for 10 minutes). For slices derived from WT mice, DHPG incubation reliably induced LTD lasting over 1 hour (Fig. 1A–C). In comparison, DHPG induced only transient LTD in slices from APP/PS1 mice (Fig. 1A–C).

Previous studies demonstrated that exogenous Aβ application results in the enhancement of NMDAR-dependent LTD (Li et al., 2009; Ma et al., 2012). To examine the effects of Aβ on mGluR-LTD, we applied DHPG to hippocampal slices pretreated with 500 nM Aβ (1-42). To our surprise, we found no significant

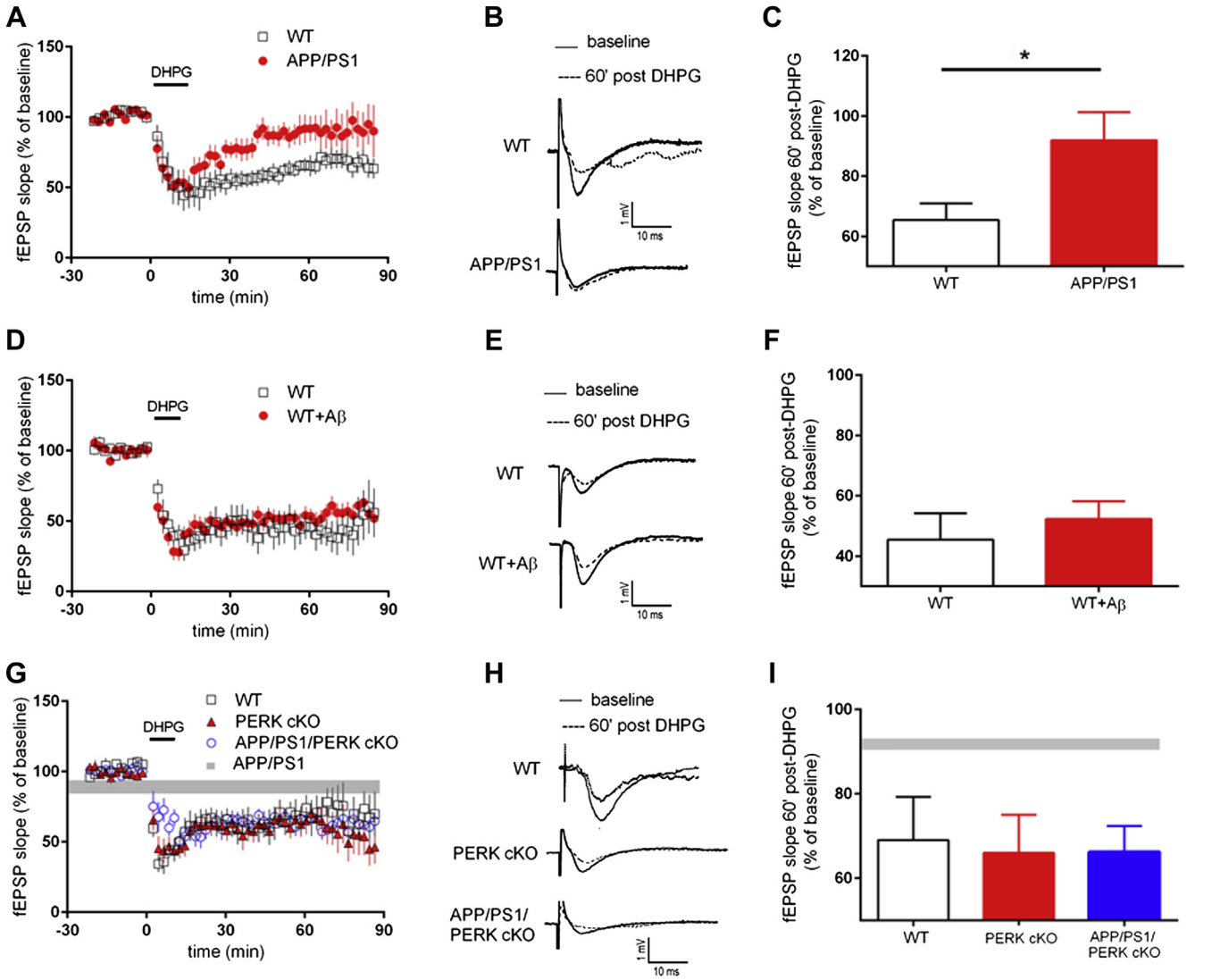


**Fig. 1.** Hippocampal mGluR-LTD is impaired in APP/PS1 mice. (A) DHPG-induced mGluR-LTD was inhibited in slices from APP/PS1 mice (filled circles), compared to WT mice (open squares). (B) Representative fEPSP traces before and after DHPG treatment to induce mGluR-LTD for the experiments shown in panel A. (C) Cumulative data showing mean fEPSP slopes 60 minutes after DHPG application for the mGluR-LTD experiments in panel A. n = 9 for WT, n = 10 for APP/PS1, $^{*}p < 0.05$, independent unpaired two-tailed *t* test. (D) DHPG induced similar mGluR-LTD in WT slices treated with either vehicle (open squares) or 500 nM Aβ1-42 (filled circles). (E) Representative fEPSP traces before and after DHPG treatment to induce mGluR-LTD for the experiments shown in panel D. (F) Cumulative data showing mean fEPSP slopes 60 minutes after DHPG application for the mGluR-LTD experiments in panel D. n = 10 for WT, n = 12 for WT + Aβ, $p = 0.51$, independent unpaired two-tailed *t* test. (G) DHPG induced normal mGluR-LTD in slices from APP/PS1/PERK cKO mice (open circles), compared to WT control mice (open squares). For comparison, mGluR-LTD data for APP/PS1 mice are shown as a horizontal gray bar. In addition, mGluR-LTD in slices from PERK cKO mice (filled triangles) was indistinct from WT control group. (H) Representative fEPSP traces before and after DHPG treatment for the mGluR-LTD experiments shown in panel G. (I) Cumulative data showing mean fEPSP slopes 60 minutes after DHPG application for the mGluR-LTD experiments shown in panel G. For comparison, mGluR-LTD data for APP/PS1 mice are shown as a horizontal gray bar. n = 9 for WT, n = 8 for PERK cKO, n = 10 for APP/PS1/PERK cKO, $p = 0.96$, one-way ANOVA. Abbreviations: Aβ, amyloid beta; ANOVA, analysis of variance; cKO, conditional knockout; fEPSP, field excitatory postsynaptic potential; LTD, long-term depression; mGluR, metabotropic glutamate receptor; WT, wild type.

difference in mGluR-LTD between slices treated with vehicle (Fig. 1D–F) and Aβ (Fig. 1D–F). Taken together, these findings indicate that mGluR-LTD is blocked in the aged, chronic AD model mice.

### 3.2. Conditional PERK gene deletion reverses mGluR-LTD failure in APP/PS1 mice

mGluR-LTD requires *de novo* protein synthesis (Hou et al., 2006; Huber et al., 2000). In addition, it was demonstrated recently that abnormal hyperphosphorylation of eIF2α due to elevated PERK activity resulted in decreased *de novo* protein synthesis in the hippocampus of AD model mice (Ma et al., 2013). Therefore, we investigated whether mGluR-LTD failure in APP/PS1 mice could be alleviated by restoring translational homeostasis via the genetic suppression of PERK. We bred mice harboring a floxed *PERK* gene with mice expressing a brain-specific *Cre* recombinase to generate mice in which PERK was conditionally removed in excitatory neurons in the forebrain late in development (PERK cKO). We further generated a mutant mouse line that expressed both *APPswe/PS1ΔE9* and homozygous *Cre PERK$^{-/-}$flox* transgenes (APP/PS1/PERK cKO), in which both eIF2α hyperphosphorylation and *de novo* protein synthesis defects in AD mice were corrected (Ma et al., 2013). We found that hippocampal mGluR-LTD was not altered significantly in PERK cKO mice (Fig. 1G–I), compared to WT control mice (Fig. 1G–I). Notably, in slices from APP/PS1/PERK cKO mutant mice,

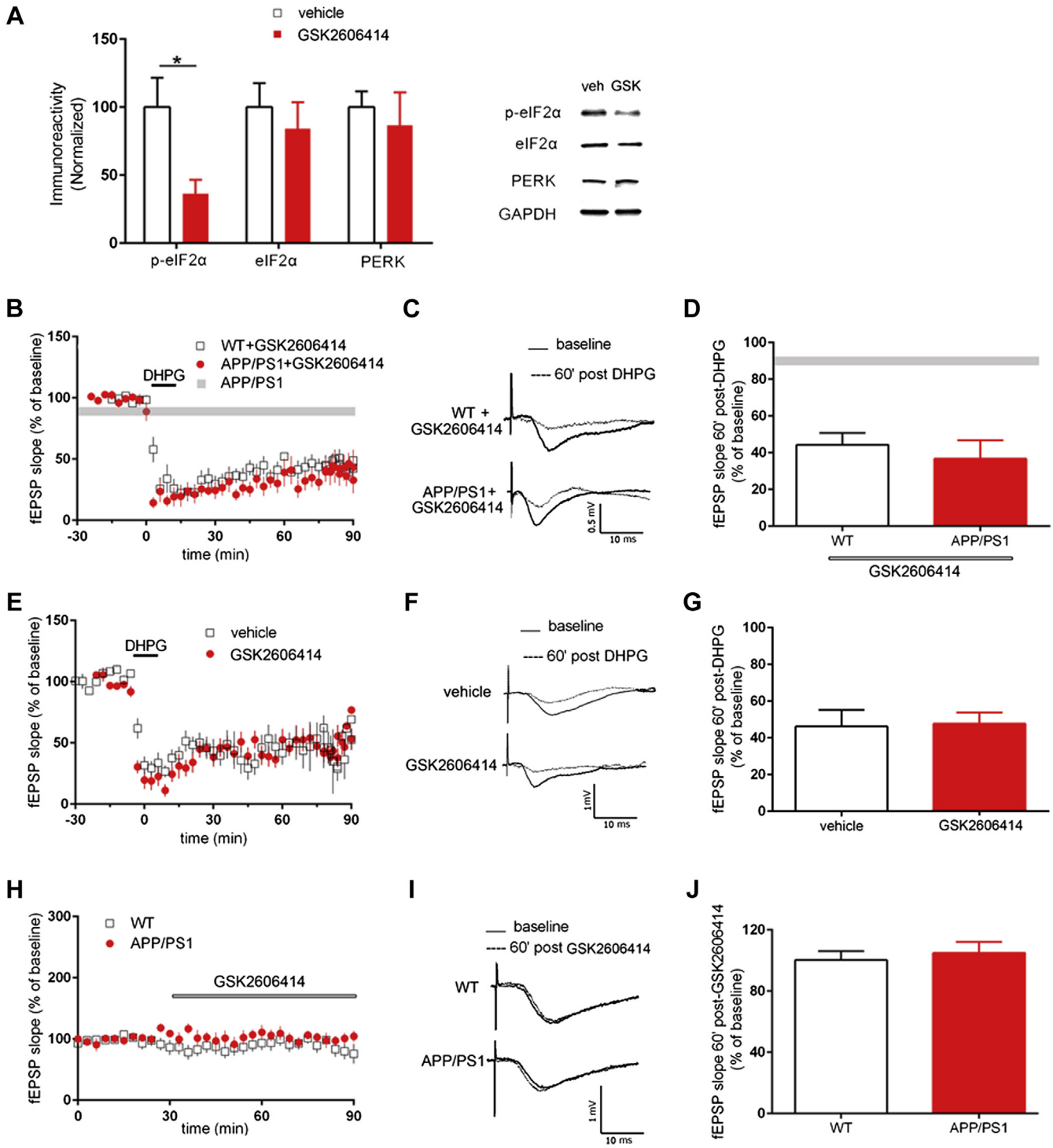


**Fig. 2.** Hippocampal mGluR-LTD impairments in APP/PS1 AD model mice are rescued by the PERK inhibitor GSK2606414. (A) Levels of phospho-eIF2α were reduced in hippocampal slices treated with GSK2606414. Levels of total eIF2α and PERK were not affected by GSK2606414; n = 6, $^*p < 0.05$, independent unpaired two-tailed *t* test. (B) In the presence of PERK inhibitor GSK2606414, DHPG induced similar LTD in slices from WT (open squares) and APP/PS1 mice (filled circles). For comparison, mGluR-LTD data for APP/PS1 mice are shown as a horizontal gray bar. (C) Representative fEPSP traces before and after DHPG treatment for the mGluR-LTD experiments shown in panel B. (D) Cumulative data showing mean fEPSP slopes 60 minutes after DHPG application for the mGluR-LTD experiments in panel B. n = 10 for WT, n = 7 for APP/PS1, $p = 0.52$, independent unpaired two-tailed *t* test. For comparison, mGluR-LTD data for APP/PS1 mice are shown as a horizontal gray bar. (E) DHPG-induced LTD was not affected in WT slices treated with GSK2606414 (filled circles), compared to vehicle-treated slices (open squares). (F) Representative fEPSP traces before and after DHPG treatment for the mGluR-LTD experiments shown in panel E. (G) Cumulative data showing mean fEPSP slopes 60 minutes after DHPG application for the mGluR-LTD experiments in panel E. n = 6 for vehicle, n = 9 for GSK2606414, $p = 0.87$, independent unpaired two-tailed *t* test. (H) GSK2606414 did not affect baseline fEPSPs. (I) Representative fEPSP traces before and after GSK2606414 treatment for experiments are shown in panel H. (J) Cumulative data showing mean fEPSP slopes 60 minutes after GSK2606414 application for the experiments in panel H. n = 12 for WT, n = 9 for APP/PS1, $p = 0.35$, independent unpaired two-tailed *t* test. Abbreviations: AD, Alzheimer's disease; eIF2, eukaryotic initiation factor 2; fEPSP, field excitatory postsynaptic potential; LTD, long-term depression; mGluR, metabotropic glutamate receptor; WT, wild type.

DHPG successfully induced mGluR-LTD that was indistinguishable from WT control mice (Fig. 1G–I). These findings suggested that suppression of eIF2α phosphorylation via the genetic removal of PERK in excitatory neurons improves AD-associated mGluR-LTD deficits.

### 3.3. Hippocampal mGluR-LTD impairments in APP/PS1 mice are rescued by a selective inhibitor of PERK

In addition to the genetic deletion of PERK, we used a pharmacological approach to examine the effects of repressing PERK/eIF2α signaling on the mGluR-LTD impairments in AD mice. Recently, it was reported that a newly characterized and specific inhibitor of PERK (GSK2606414) rescued memory deficits and brain pathology in a mouse model of prion disease (Moreno et al., 2013), and brain pathology in a mouse model of frontotemporal dementia (Radford et al., 2015). Notably, in both of these studies, the rescuing effects of the PERK inhibitor were associated with inhibition of PERK/eIF2α signaling and restored levels of protein synthesis (Moreno et al., 2013; Radford et al., 2015). We first demonstrated that treatment of slices with GSK2606414 caused reduction of eIF2α phosphorylation, but did not affect levels of total eIF2α or PERK (Fig. 2A). Moreover, in slices from APP/PS1 mice treated with GSK2606414, DHPG-induced mGluR-LTD (Fig. 2B–D) was indistinguishable from WT control slices treated with the inhibitor (Fig. 2B–D). We further demonstrated that GSK2606414 by itself did not alter mGluR-LTD in WT slices (Fig. 2E–G) when compared to vehicle-treated WT slices (Fig. 2E–G). In addition, the PERK inhibitor did not alter basal synaptic function in either WT or APP/PS1 mice, as indicated by the findings that neither fEPSP baseline nor synaptic input-output relationships was affected by GSK2606414 (Fig. 2H–J, and data not shown). Taken together, mGluR-LTD failure in APP/PS1 AD model mice can be rescued by PERK inhibitor GSK2606414.

## 4. Discussion

Long-lasting forms of synaptic plasticity including LTP and LTD remain the prime molecular mechanisms associated with learning and memory (Malenka and Bear, 2004). This is consistent with the notion that AD, the most common form of dementia in elderly, has been called a disease of "synaptic failure" (Selkoe, 2002). Numerous studies have indicated that deficiencies in neuronal plasticity characterize an early and sustaining key pathophysiology in AD (Ma and Klann, 2012). Consequently, elucidation of the detailed molecular mechanisms by which the neuronal plasticity impairments occur may present important opportunities for therapeutic discoveries. Here, we describe for the first time that mGluR-LTD, a form of synaptic plasticity implicated in cognitive function mechanisms (Lüscher and Huber, 2010), is inhibited in an aged AD mouse model. Importantly, AD-associated inhibition of mGluR-LTD was reversed by repressing the eIF2α kinase PERK with either genetic or pharmacological approaches.

Many studies have demonstrated that Aβ impacts both LTP (inhibition) and LTD (enhancement) that are NMDAR dependent (Li et al., 2009; Ma et al., 2014; Shankar et al., 2008). In contrast, we found that exogenous Aβ application does not affect mGluR-LTD (Fig. 1D–F). Besides factors that might be attributed to Aβ sources (synthetic vs. human extracts) and preparation (different oligomer species), our findings suggest that acute Aβ application targets mainly at signaling pathways that are connected to NMDAR-dependent neuronal plasticity. In contrast, hippocampal mGluR-LTD was impaired in aged APP/PS1 AD model mice (Fig. 1A–C), indicating that the chronic accumulation of Aβ with aging impairs cellular mechanisms underlying mGluR-LTD. One such mechanism could be *de novo* protein synthesis, which is essential for long-lasting synaptic plasticity, including both LTP and LTD, regardless of whether they are NMDAR or mGluR dependent (Richter and Klann, 2009). In agreement with this concept, repression of eIF2α kinase PERK in APP/PS1 mice, which improves *de novo* protein synthesis (Ma et al., 2013), can alleviate AD-associated mGluR-LTD defects (Fig. 1G–I and Fig. 2). Of interest, it was reported that hippocampal mGluR-LTD was enhanced in PERK cKO mice at young ages (4–5 weeks; Trinh et al., 2014). In contrast, here we observed normal mGluR-LTD in old (12–15 months) PERK cKO mice (Fig. 1G–I), suggesting aging-related alterations in the synaptic response to DHPG when PERK/eIF2α signaling is repressed. It also should be noted that to induce mGluR-LTD in aged mice, DHPG must be applied to slices at a concentration of 100 μM, compared to 50 μM DHPG used in young mice (Trinh et al., 2014). Therefore, the relatively high-dose DHPG might cause a "ceiling" effect at synapses so that the activation of mGluR is either maximized or saturated, which is associated with the blunting of mGluR-LTD enhancement in PERK cKO mice (Fig. 1G–I) and WT mice treated with the PERK inhibitor (Fig. 2). The four kinases for eIF2α (PERK, GCN2, PKR, and HRI) were initially categorized and named for their response to a different cellular stress associated with activation of a single kinase (Wek et al., 2006). However, accumulating evidence indicates that in situations such as oxidative stress, which is linked to AD pathogenesis, multiple eIF2α kinases (especially PERK and GCN2) are recruited either simultaneously or sequentially to help maintain cellular homeostasis (Hamanaka et al., 2005; Zhan et al., 2004). In agreement with this idea, genetically reducing the expression of either PERK or GCN2 was shown to improve NMDAR-LTP impairments in AD mice (Ma et al., 2013). Meanwhile, PERK appears to play a dominant role in controlling eIF2α activity in brain based on the findings that basal levels of eIF2α phosphorylation are decreased by PERK deletion but not by removal of genes for other eIF2α kinases such as GCN2 or PKR (Ma et al., 2013). Although future investigation of aging-dependent alterations in translational control via each of the eIF2α kinases is still required, therapeutics that normalize eIF2α phosphorylation has potential for treatment of AD and other neurodegenerative disorders.

## Disclosure statement

The authors declare no conflict of interest.

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