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Molecules and Cells

Pathway-Specific Alteration of Synaptic Plasticity in Tg2576 Mice

Jung Hoon Jung, Kyongman An, Oh Bin Kwon, Hye-sun Kim[1], and Joung-Hun Kim*

Various animal models of Alzheimer disease (AD) are characterized by deficits in spatial memory that are causally related to altered synaptic function and impairment of long-term potentiation (LTP) in the hippocampus. In Tg2576 AD mice, we compared LTP in 2 major hippocampal pathways, Schaffer collateral (SC) and mossy fiber (MF) pathways. Whereas LTP was completely abolished in the SC pathway of Tg2576 mice, we found no decrease in LTP induced by stimulation of the MF pathway. In fact, we found that in the MF pathway, LTP was slightly, but significantly, enhanced compared with that in the MF pathway of WT littermates. This pathway-specific impairment of LTP is not attributable to alterations in transmitter release, as indicated by an unaltered paired-pulse ratio. These results suggest that the spatial memory deficits normally seen in AD models arise primarily from LTP impairment at the SC pathway.

INTRODUCTION

Alzheimer disease (AD) is characterized by a gradual loss of neurons and synapses in various brain areas (Jacobsen et al., 2006; Morrison and Hof, 1997) as well as pathological markers such as senile plaques and neurofibrillary tangles (Duyckaerts et al., 2009; Ondrejcak et al., 2010). However, the etiological mechanisms of this devastating disease remain largely inconclusive. For instance, amyloid β (Aβ), a major component of senile plaques has been shown to cause neuronal cell death (Duyckaerts et al., 2009), but extensive clinical surveys have indicated only a mere relationship between the abundance of Aβ and the severity of AD (Barber, 2010).

The hippocampus is a brain region that exhibits early ab-normalities in AD patients, and it is also critically involved in the acquisition and retention of spatial memory (Chapman et al., 1999; Morrison and Hof, 1997; Ondrejcak et al., 2010; Rowan et al., 2003). The intrinsic circuitry within the hippocampus comprises schaffer collateral (SC), mossy fiber (MF) and perforant path (PP) pathways. These trisynaptic pathways have been considered to control animal behaviors and regulate hippocampus-dependent memories. Indeed, selective lesions of either dentate gyrus (DG) (Sutherland et al., 1983), CA3 (Sutherland et al., 1983), or CA1 (Langston et al., 2010) cause deficits in spatial memory which are similar but slightly different from those derived from a complete lesion of the whole hippocampus. Further analyses indicate that the DG is important for spatial orientation performance (Xavier and Costa, 2009) and the CA3 is required for spatial memory formation and subsequent retrieval (Gilbert and Brushfield, 2009), whereas the CA1 region is more involved in the temporal component of task (Langston et al., 2010). Therefore, it is conceivable that the MF pathway between DG and CA3 is critical for the appropriate expression of spatial memory. Despite this possible correlation between the MF pathway and memory retention, the pathophysiological role of this pathway in AD models is rarely examined in the context of the induction and maintenance of LTP and spatial memory, although the functional contributions of the SC and PP have been extensively studied.

A number of genetically modified animal models have been generated to phenocopy at least some AD symptoms (Chapman et al., 1999; Saura et al., 2004; Wang et al., 2010). Tg2576 mice, the most widely used AD model animal harboring the human APPswe695 gene, exhibits early synaptic abnormalities starting around the age of 4-6 months and displays several neuropathological features of AD later in its life (D'Amelio et al., 2011; Jacobsen et al., 2006). Importantly, previous studies demonstrated a clear loss of long-term potentiation (LTP) at either the SC or PP pathways of Tg2576 mice (Chapman et al., 1999; Jacobsen et al., 2006). However, it remains unclear whether LTP induction and maintenance would be affected at the MF pathway in the same mouse model, especially in animals of the ages that most closely correspond to the early stages of AD (11-13 months). Furthermore, previous studies with Tg2576 mice have involved varying experimental conditions, including recording from different brain areas and usage of different LTP induction paradigms. Because of this empirical inconsistency, it is difficult to directly compare previous results and determine whether individual hippocampal pathways are similarly affected in this mouse model or which pathway is more sensitive to LTP blockade.

To address these problems, we performed extracellular field recordings while stimulating either the SC or MF pathway of hippocampal slices acutely prepared from both 12-13 month-old Tg2576 mice and wild type (WT) littermates. We then,

Department of Life Science, Pohang University of Science and Technology (POSTECH), Pohang 790-784, Korea, [1]Department of Pharmacology, Seoul National University, College of Medicine, Seoul 110-799, Korea
*Correspondence: joungkim@postech.ac.kr

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compared basal synaptic transmission, short-term synaptic plasticity by measuring paired-pulse ratios (PPR), and long-term synaptic plasticity by assessing LTP. We found that LTP was impaired in the SC pathway, but was enhanced in the MF pathway of Tg2576 mice.

MATERIALS AND METHODS

Animals

Male Tg2576 (HuAPP695SWE) mice from Taconic (USA) were crossed with a C57BL/6J × SJL F1 hybrid line, and the offspring were genotyped. Heterozygous transgenic and WT littermate mice were used. Animals were housed under a 12-hour light/dark cycle and given *ad libitum* access to food and water. All procedures for animal experiments were performed in accordance with POSTECH guidelines on animal care and use.

Electrophysiology

Brains were quickly removed and chilled in ice-cold 50% sucrose-based (175 sucrose, 11 glucose, 20 NaCl, 3.5 KCl, 1.4 NaH_2PO_4, 1.3 $MgCl_2$, and 26 $NaHCO_3$ in mM) artificial cerebrospinal fluid (aCSF) (10 glucose, 119 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 1.3 $MgSO_4$, 2.5 $CaCl_2$, and 26 $NaHCO_3$ in mM) that was oxygenated with 95% O_2 and 5% CO_2 gas. Coronal hippocampal slices (350 μm thick) were prepared using a Vibratome (Leica VT1000S, Germany) and stabilized in aCSF for more than 60 min before recording. Then, the slices were perfused with aCSF and maintained at room temperature during the recording period. For input-output curves, repeated stimulation ranging from 0 to 200 μA was applied via bipolar concentric electrodes (WPI, USA). The pulses were generated with an A360 stimulus isolator (WPI) at an interval of 30 s and field excitatory postsynaptic potentials (fEPSPs) were recorded with an Axopatch 200A amplifier linked to a Digidata 1200 (Molecular Devices, USA) interface. Test stimuli were delivered at a frequency of 0.05 Hz. To induce LTP, 4 trains of high-frequency stimulation (HFS) (100 Hz stimuli for 1 s) were delivered at an intertraining interval of 10 s after establishing a baseline for more than 20 min. In order to confirm fEPSPs induced at MF pathway, we perfused the slice with 1 μM (2S, 2′R, 3′R)-2-(2′, 3′)-dicarboxy cyclopropyl glycine (DCG-IV, Tocris Bioscience, UK) after the end of each experiment set, demonstrating that the fEPSPs were elicited by stimulation of the MF pathway (Wang et al., 2010).

Statistics

We performed Mann-Whitey tests to compare results, using SPSS 14 (SPSS Korea, Korea). All values reported are means ± SEM, and the statistical significance is indicated with asterisks indicating *P* values of < 0.05 (*), < 0.01 (**), and < 0.001 (***).

RESULTS

Numerous studies using AD animal models have revealed alterations in synaptic transmission, presumably due to various underlying causes (defects of synaptic development, presynaptic release probability changes, or abnormal trafficking of postsynaptic receptors) (Almeida et al., 2005; Moreno et al., 2009; Saura et al., 2004; Snyder et al., 2005). In order to assess possible differences in synaptic transmission in both of the studied pathways, we measured fEPSPs that responded to increasing stimulus intensity delivered to either the SC or MF pathway. The fEPSPs elicited by stimulation of either the SC or MF pathway displayed typical responses; the traces of fEPSPs elicited by stimulation of the MF pathway was sharper than that of fEPSPs evoked at the SC pathway, and the maximal amplitude of fEPSPs evoked by stimulation of the SC pathway was generally greater than that of fEPSPs evoked at the MF pathway (Figs. 1B and 1D); (Bukalo and Dityatev, 2006). The stimulus ranges were from 0 to 160 μA for the SC pathway and from 0 to 120 μA for the MF pathway. We perfused the slice with DCG-IV (1 μM) after completion of recording to ascertain whether the fEPSPs were produced by stimulation of MF pathway. Only when the mean amplitude of fEPSPs was reduced by more than 70% by DCG-IV, the data were included for analysis (data not shown). The input-output relationships obtained at either pathway did not differ between Tg2576 and WT mice (Fig. 1), consistent with previous reports that the Tg2576 mouse do not have a defect in basal synaptic transmission (Chapman et al., 1999; Witton et al., 2010). Because we did not observe any defect in basal synaptic transmission, we subsequently investigated whether Tg2576 mice had any alterations in synaptic plasticity.

Previous studies have provided evidence that the memory loss normally observed in Tg2576 mice is associated with defects in circuits and connectivity of forebrain structures (Jacobsen et al., 2006; Ondrejcak et al., 2010; Ribaut-Barassin et al., 2003), but the early behavioral phenotypes that do not accompany neuronal loss are primarily due to synaptic dysfunction in the hippocampal regions (Chapman et al., 1999; Jacobsen et al., 2006; Morrison and Hof, 1997; Ondrejcak et al., 2010). We attempted to trigger LTP in both the SC and MF pathways by the application of an identical stimulation protocol: 4 trains of HFS (100 Hz, 1 s) with an inter-training interval of 10 s. This stimulation protocol has been known to lead to a stable and persistent enhancement of fEPSPs (Nagy et al., 2006; Wojtowicz and Mozrzymas, 2010). In the SC pathway of Tg2576 mice, LTP was almost completely absent at 60 min after HFS application, whereas WT mice exhibited significant increases in fEPSP amplitudes compared to those recorded at baseline (WT, 165.3% ± 11.0% *vs.* Tg2576, 102.4% ± 5.1%, ***p < 0.001; Figs. 2A-2C). We also observed a significant reduction in LTP at the SC pathway of Tg2576 mice at 10 min after stimulation (WT, 174.3% ± 11.05% *vs.* Tg2576, 122.4% ± 4.2%, ***p < 0.001; Figs. 2A-2C). The loss of LTP is consistent with previous reports based on the same animal model, although the ages of the previously studied animals differed from those used in our study (Chapmane et al., 1999; Jacobsen et al., 2006). We also induced LTP at the MF pathway. In contrast to the results obtained from stimulation of the SC pathway, we found that the persistent LTP was produced at the MF pathway of both Tg2576 and WT mice (Figs. 2D-2E). Intriguingly, the magnitude of LTP was slightly but significantly increased in Tg2576 mice, relative to that measured in WT mice [at 10 min: WT, 145.5% ± 4.7% *vs.* Tg2576, 175.7% ± 10.3% (p < 0.05); at 60 min: WT, 132.8% ± 4.4% *vs.* Tg2576, 158.6% ± 8.5% (p < 0.01)]. These results suggest that the molecular mechanism(s) for the induction and maintenance of LTP in the MF pathway are not disturbed by the overproduction of APP and that there are unknown mechanisms that enhance LTP induction.

To elucidate mechanisms of the distinct impairment of LTP by APP overexpression, we tested short-term synaptic plasticity by PPR, which would report a change in transmitter release from presynaptic terminals (Doussau et al., 2010). Either pathway was stimulated at increasing paired-pulse intervals from 20 ms to 200 ms. However, a comparison of PPRs at the 50 ms interval showed no significant difference between Tg2576 and WT mice [SC: WT, 1.22 ± 0.09 *vs.* Tg2576, 1.16 ± 0.03 (p = 0.58); MF: WT, 1.21 ± 0.04 *vs.* Tg2576, 1.15 ± 0.03 (p = 0.36)]

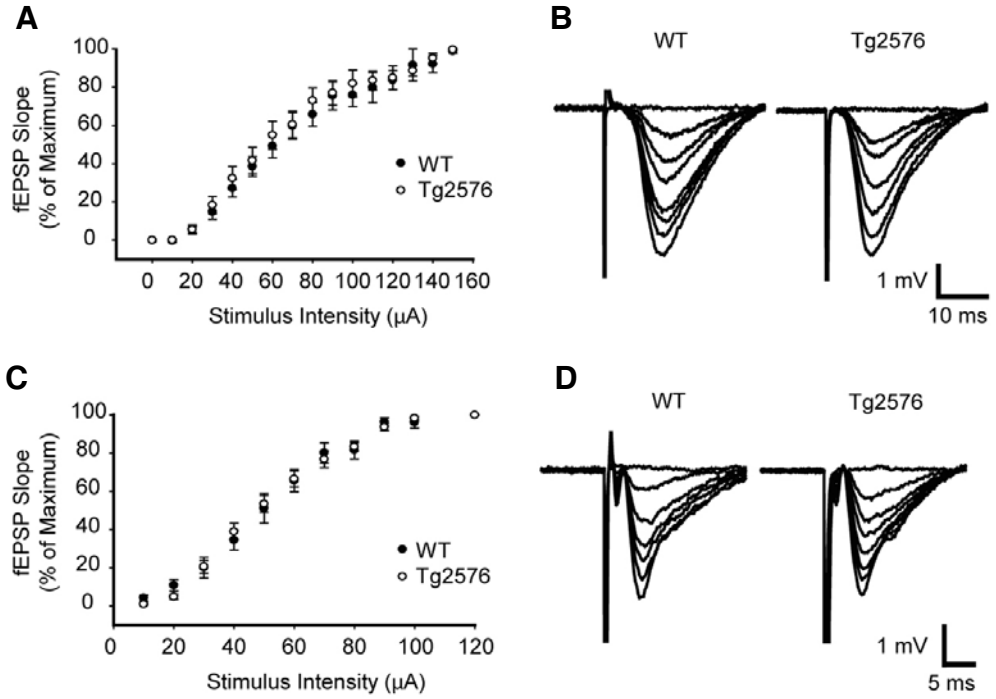

Fig. 1. Basal synaptic transmission in the SC and MF pathways is not altered in Tg2576 mice. (A) Slopes of fEPSPs elicited in the SC pathway are normalized to baseline levels. Input-output curves were obtained from 9 (4 animals) and 11 (5 animals) hippocampal slices from WT and Tg2576 mice, respectively. Triplicate fEPSPs were recorded with a 30-s delay at the indicated stimulus intensity, and these values were averaged for the analysis. (B) Representative traces from WT and Tg2576 mice are illustrated by overlaying each fEPSP response to the stimulus from 0 to 160 μA. (C) Slopes of fEPSPs elicited in the MF pathway are normalized to baseline levels. Input-output curves were obtained from 12 (4 animals) and 16 (5 animals) slices from WT and Tg2576 mice, respectively. Triplicate fEPSPs were recorded with a 30-s delay at the indicated stimulus intensity, and these values were averaged for the analysis. (D) Representative traces from WT and Tg2576 mice are illustrated by overlaying each fEPSP response to the stimulus from 0 to 120 μA.

(Fig. 3). The PPRs observed at the other time intervals were also not distinguishable between groups (data not shown). Thus, alteration in transmitter release probability does not account for the observed difference in induction and maintenance of LTP between Tg2576 and WT mice. Along with the unaltered input-output relationship (Fig. 1), this PPR result suggests that the overproduction of APP selectively affects postsynaptic targets involved in LTP at the SC pathway, possibly *N*-methyl-D-aspartate receptors (NMDARs) as previously suggested (Bukalo and Dityatev, 2006; Saura et al., 2004; Snyder et al., 2005).

DISCUSSION

Aβ and its oligomeric forms lead to synaptic dysfunction, which results in a decrease in cognitive ability in both AD patients and animal models, particularly in the early stages (Jacobsen et al., 2006; Ondrejcak et al., 2010; Rowan et al., 2003). However, it remains unclear which hippocampal pathway is the most sensitive to an abundance of Aβ. Here, we provide evidence that LTP at the SC pathway is impaired in an APP-overexpressing model, whereas LTP can still be induced in the MF pathway in the same animal model. Moreover, this differential impairment of LTP accompanies both normal baseline synaptic transmission and neurotransmitter release from presynaptic terminals.

Although we observed normal LTP in the MF pathway, it was recently reported that LTP in the MF pathway was significantly impaired in Tg2576 mice (Witton et al., 2010). This discrepancy seems to be due to differences in experimental conditions. For example, previous studies were based on EPSP and LTP recordings obtained from more aged animals, such as 24-month-old mice with Aβ plaques (Chapman et al., 1999; Hsiao et al., 1996; Kawarabayashi et al., 2001; Witton et al., 2010). It is plausible that these older animals represent the more advanced stages of AD, but not the early stages that typically do not show neuronal loss (Kawarabayashi et al., 2001). Therefore, the impairment of LTP in the SC pathway is likely to cause early cognitive dysfunction in Tg2576 mice. However, we cannot exclude the possibility that the slight enhancement of LTP in the MF pathway could also be involved in the behavioral changes observed Tg2576 mice. It will be extremely interesting to examine whether the increased LTP in the MF pathway affects the cognitive ability of Tg2576 mice, because this would further extend our understanding of the functional role of each of these circuits in behavior.

How is LTP differentially altered between the SC and MF pathways of Tg2576 mice? It is well documented that LTP elicited by stimulation of the SC pathway is dependent on activation of NMDARs, but this is not the case in the MF pathway (Bukalo and Dityatev, 2006). Aβ specifically disrupts a number of NMDAR-related signaling pathways such as the Ca^{2+}-dependent protein phosphatase calcineurin, cAMP response element-binding protein (CREB), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and protein phosphatase 1 (Yamin, 2009). Moreover, Aβ inhibits NMDAR-mediated synaptic transmission by affecting the NMDAR trafficking at the synapse; this causes synaptic dysfunction and impairment of NMDAR-dependent LTP (Snyder et al., 2005). Therefore, our findings support the hypothesis that NMDARs in the SC pathway of Tg2576 mice

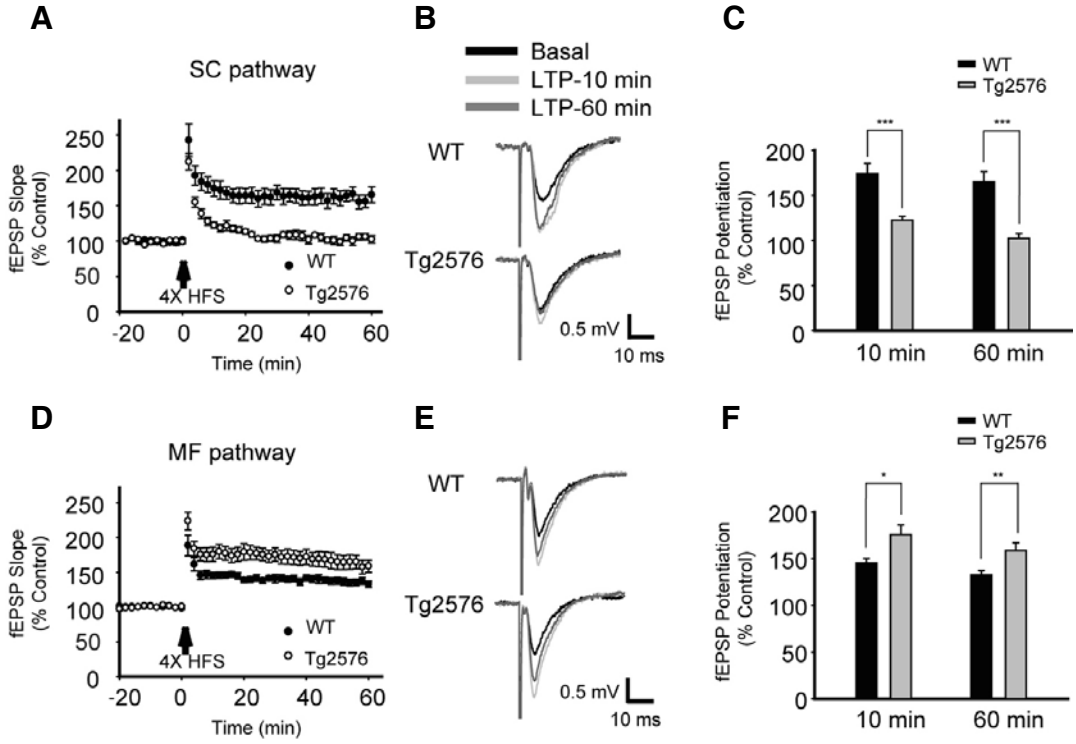

Fig. 2. LTP regulation differs between the SC and MF pathways of Tg2576 mice. (A) LTP results in the SC pathway of WT and Tg2576 mice are shown. fEPSP slopes (mV/ms) are normalized to the baseline levels that were recorded for 20 min before HFS stimulation. LTP induced by 4 trains of HFS was impaired in Tg2576 mice (9 slices from 4 animals), compared to WT mice (8 slices from 3 animals). Each point represents the mean slopes of 6 fEPSPs. (B) Representative traces from the SC pathway experiment are illustrated at the indicated time points. The black line is the baseline trace, the light gray line is the trace at 10 min (induction), and the dark gray line is the trace at 60 min (maintenance) after the HFS stimulation. (C) A summary histogram for LTP levels at 10 and 60 min is shown for the SC pathway of WT and Tg2576 mice (***$p < 0.001$ for both time points). (D) LTP results in the MF pathway of WT and Tg2576 mice are shown. fEPSP slopes (mV/ms) are normalized to baseline levels that were recorded for 20 min before HFS stimulation. LTP induced by 4 trains of HFS was slightly enhanced in Tg2576 mice (10 slices from 5 animals), compared to WT mice (13 slices from 5 animals). Each point represents the mean slopes of 6 fEPSPs. (E) Representative traces from the MF pathway experiment are illustrated at the indicated time points. The black line is the baseline trace, the light gray line is the trace at 10 min (induction), and the dark gray line is the trace at 60 min (maintenance) after the HFS stimulation. (F) A summary histogram for LTP levels at 10 and 60 min is shown for the MF pathway of WT and Tg2576 mice (*$p < 0.05$ for 10 min and **$p < 0.01$ for 60 min).

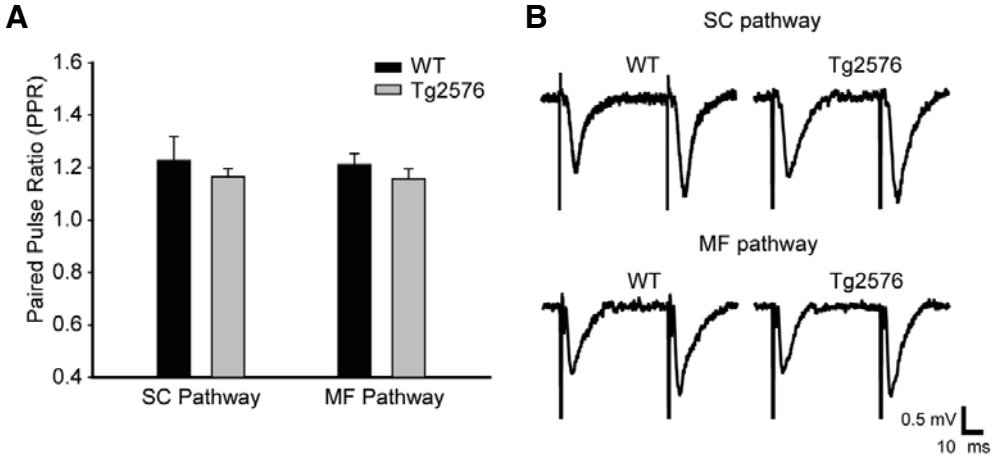

Fig. 3. Short-term plasticity is not impaired in Tg2576 mice. (A) A summary histogram for PPR values measured at the 50-ms interval. Amplitudes of the second fEPSP are divided by those of the first response, and the resultant ratios are compared between genotypes. (B) Representative traces of paired stimulation in the SC and MF pathways are depicted after averaging triplicate traces for clarity.

are a major molecular target of Aβ, whose dysfunction results in a decrease in cognitive function, because LTP in MF synapses is typically NMDAR-independent. Thus far, we do not have any evidence to explain how LTP in the MF pathway is enhanced in Tg2576 mice. Newly-born granule cells would be more abundant in DG of PDGF-$APP_{SW,Ind}$ mice compared to those of WT mice (Jin et al., 2004). Because the newly-generated granule cells could increase GABAergic transmission (Lledo et al., 2006), an increased level of GABA signaling at MF synapses could potentially activate presynaptic $GABA_A$ receptors, which facilitates and enhances the induction efficacy of LTP (Ruiz et al., 2010). This scenario and the functional role of LTP in the MF pathway warrant further investigation.

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