Brief Communications

The BDNF Val66Met Polymorphism Impairs NMDA Receptor-Dependent Synaptic Plasticity in the Hippocampus

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The Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene results in a defect in regulated release of BDNF and affects episodic memory and affective behaviors. However, the precise role of the BDNF Val66Met polymorphism in hippocampal synaptic transmission and plasticity has not yet been studied. Therefore, we examined synaptic properties in the hippocampal CA3–CA1 synapses of $BDNF^{Met/Met}$ mice and matched wild-type mice. Although basal glutamatergic neurotransmission was normal, both young and adult mice showed a significant reduction in NMDA receptor-dependent long-term potentiation. We also found that NMDA receptor-dependent long-term depression was decreased in $BDNF^{Met/Met}$ mice. However, mGluR-dependent long-term depression was not affected by the BDNF Val66Met polymorphism. Consistent with the NMDA receptor-dependent synaptic plasticity impairment, we observed a significant decrease in NMDA receptor neurotransmission in the CA1 pyramidal neurons of $BDNF^{Met/Met}$ mice. Thus, these results show that the BDNF Val66Met polymorphism has a direct effect on NMDA receptor transmission, which may account for changes in synaptic plasticity in the hippocampus.

Introduction

Brain-derived neurotrophic factor (BDNF), a neurotrophin highly expressed in the hippocampus, has been implicated in hippocampus-dependent cognitive functions (Hariri et al., 2003; Bekinschtein et al., 2008). Consistent with this role, BDNF modulates synaptic neurotransmission, neuronal excitability, and synaptic plasticity (Korte et al., 1995; Patterson et al., 1996; Tyler and Pozzo-Miller, 2001; Yano et al., 2006). Also, mice lacking the BDNF receptor, TrkB, and mice with targeted mutation in the PLCγ site of TrkB show abnormal hippocampal long-term potentiation (LTP) (Minichiello et al., 1999, 2002).

A role for BDNF in learning and memory is further supported by the recent finding that the BDNF Val66Met polymorphism impairs episodic memory and hippocampal function (Egan et al., 2003; Hariri et al., 2003; Chen et al., 2006). Recently, it was reported that the BDNF Val66Met polymorphism alters fear extinction learning in both humans and mice (Soliman et al., 2010). The BDNF Val66Met polymorphism affects intracellular trafficking of pro-BDNF and alters the regulated release of BDNF (Egan et al., 2003; Chen et al., 2006). Measurement of BDNF levels in $BDNF^{Met/Met}$ mice revealed ~30% reduction in regulated release of BDNF (Chen et al., 2006). This BDNF release abnormality is likely to be due to the altered binding of $BDNF^{Met}$ to sortilin, a sorting protein that interacts with BDNF in the prodomain region (Chen et al., 2005).

A variety of studies have implicated the BDNF Val66Met polymorphism in neuropsychiatric disorders such as schizophrenia, Alzheimer's disease, and affective disorders (Ventriglia et al., 2002; Chen et al., 2006; Rybakowski, 2008; Verhagen et al., 2010). Although these studies suggest a correlative role for BDNF in hippocampal functions, whether an impairment in the regulated release of BDNF affects synaptic neurotransmission and plasticity in the hippocampus has not been explored in depth. We therefore examined whether the BDNF Val66Met polymorphism affects synaptic plasticity at the CA3–CA1 synapses using $BDNF^{Met}$ knock-in mice ($BDNF^{Met/Met}$). We find that $BDNF^{Met/Met}$ mice exhibit a decrease in hippocampal synaptic plasticity that depends upon the activation of NMDA receptors.

Materials and Methods

Animals. $BDNF^{Met/Met}$ mice were maintained on an inbred C57BL/6 background (Chen et al., 2006). $BDNF^{Met/Met}$ female mice and wild-type littermates derived from heterozygous $BDNF^{+/Met}$ parents were used for all experiments. All animals were kept on a 12:12 light–dark cycle at 22°C with food and water available *ad libitum*. All experiments were performed in accordance with institutional guidelines. Mice were genotyped as described previously (Chen et al., 2006).

Field EPSP recording. Mice were decapitated after pentobarbital anesthesia. Brains were quickly removed and hippocampi were cut into 300 μm transverse slices with a tissue chopper and maintained at room temperature for 90 min in a brain slice keeper before transferring to an interface recording chamber maintained at 32°C in artificial CSF (ACSF)

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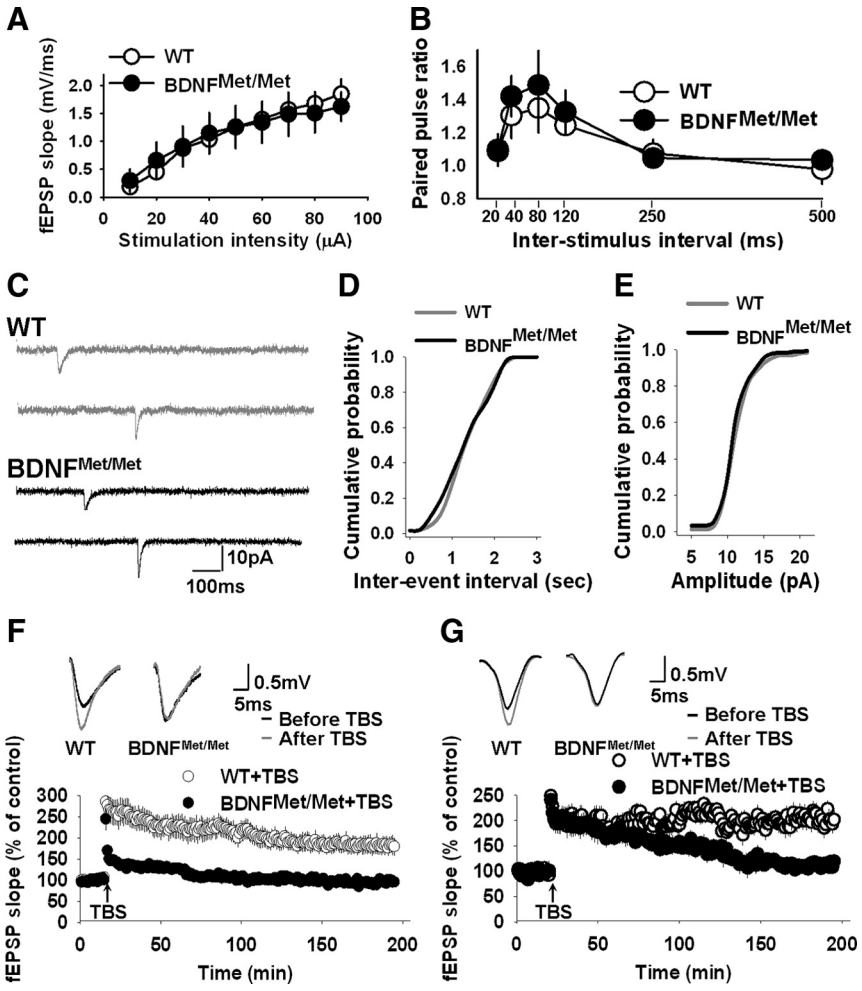

Figure 1. Basal synaptic neurotransmission and PPF are normal but LTP is impaired at the CA3–CA1 synapses of BDNF$^{Met/Met}$ mice. ***A***, Input–output curves of the CA3–CA1 fEPSPs in 4-month-old BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). ***B***, Paired-pulse ratios of the CA3–CA1 fEPSPs in 4-month-old BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). ***C***, Examples of mEPSCs in BDNF$^{Met/Met}$ ($n = 10$) and matched wild-type mice ($n = 10$). ***D***, ***E***, Cumulative probability distribution of interevent interval (***D***) and amplitude (***E***) of mEPSCs in BDNF$^{Met/Met}$ and matched wild-type mice. ***F***, TBS-induced LTP at the CA3–CA1 synapses of 1-month-old BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 7$). ***G***, TBS-induced LTP at the CA3–CA1 synapses of 4-month-old BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). BDNF$^{Met/Met}$ and wild-type groups that did not receive TBS showed stable fEPSP slope during the course of recording. Inset, Examples of fEPSP recordings before TBS and at 180 min after TBS.

consisting of the following (in mM): NaCl (118), KCl (4.5), glucose (10), NaH_2PO_4 (1), $CaCl_2$ (2), $MgCl_2$ (2), and $NaHCO_3$ (25) (aerated by 95% O_2/5% CO_2, pH 7.4). CA1 field EPSPs (fEPSPs) were recorded with a glass electrode filled with 2 M NaCl by stimulating the Schaffer collateral fibers through a concentric bipolar electrode (FHC). Basal synaptic neurotransmission was studied by plotting stimulus strength against fEPSP slope to generate input–output relations. Paired-pulse facilitation (PPF) was defined as the second slope divided by the first. For the LTP and long-term depression (LTD) measurements, a 15 min baseline was recorded every minute at an intensity that evoked a response ~35% of the maximum response. LTP was induced using a theta-burst stimulation (TBS, 4 pulses at 100 Hz, with the bursts repeated at 5 Hz and each tetanus including three 10-burst trains separated by 15 s) (Serulle et al., 2007). LTD was induced by application of 900 pulses at 1 Hz (Massey and Bashir, 2007). (*S*)-3,5-Dihydroxyphenylglycine hydrate (DHPG)-LTD was induced by bath perfusion of DHPG (100 μM) for 10 min (Fitzjohn et al., 1999; Kumar and Foster, 2007).

Whole-cell recording. Postnatal day 21 (P21)–P25 mice were killed by decapitation. The brains were quickly removed and placed in ice-cold ACSF consisting of the following (in mM): NaCl (118), KCl (2.5), $CaCl_2$ (3), $MgCl_2$ (1), $NaHCO_3$ (26), NaH_2PO_4 (1), and D-glucose (10), osmolarity adjusted to 325 mOsm and aerated by 95% O_2/ 5% CO_2, pH 7.4. Transverse hippocampal slices (300 μm) were cut using a vibratome (Campden Instruments) and kept submerged in ACSF in a slice preincubator at room temperature for at least 1 h to allow for recovery. A single slice was then transferred to a recording chamber in which it was held submerged by a nylon net at 32°C with a TC324B in-line solution heater and controller (Warner Instruments). The chamber was continuously perfused by ACSF at a constant rate of 2 ml/min. The CA1 pyramidal neurons were visualized using video-enhanced infrared differential interference contrast microscopy (Hamamatsu C5405) with an Olympus BX50WI upright microscope fitted with 40× long working distance water-immersion objective. Patch electrodes (4–6 MΩ) were filled with an intracellular pipette solution consisting of the following (in mM): CsCl (145), HEPES (10), EGTA (0.5), QX-314 (5), and MgATP (5). Osmolarity was adjusted to 290 mOsm with sucrose, and pH was adjusted to 7.4 with CsOH. NMDA EPSCs were recorded at +40 mV in the presence of glycine (1 μM), $GABA_A$ receptor antagonist bicuculline (10 μM), and AMPA receptor antagonist NBQX (10 μM, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide disodium salt). Non-NMDA EPSCs were recorded at −60 mV in the presence of bicuculline (10 μM) and NMDA receptor antagonist D-APV (50 μM). Recordings were made using an Axopatch 200B amplifier (Molecular Devices) and digitized by Digidata 1440 A (Molecular Devices). Stimulating electrodes (concentric bipolar electrodes, FHC) were placed at the Schaffer collaterals to evoke EPSCs every 20 s using a Digital stimulator PG4000A (Cygnus Technology) and stimulus isolator A365 (World Precision Instruments). Miniature EPSCs (mEPSCs) were recorded in the presence of bicuculline (10 μm) and tetrodotoxin (1 μm) using an electrode solution containing the following (in mm): potassium gluconate (130), KCl (10), $MgCl_2$ (5), MgATP (5), EGTA (0.5), HEPES (5), osmolarity adjusted 290 mOsm with sucrose and pH adjusted to 7.4 with KOH. Recordings were rejected when series resistance or holding current changed by 10%.

Statistics. Results were expressed as mean ± SEM. Two-way ANOVA followed by *post hoc* comparison was used for statistical analysis. The level of significance was $p < 0.05$.

Results

CA3–CA1 LTP is altered in BDNF$^{Met/Met}$ mice

As the BDNF Val66Met polymorphism has been associated with impairments in hippocampus-dependent memory (Egan et al., 2003; Chen et al., 2006), we examined whether BDNF$^{Met/Met}$ mice showed any effect on basal synaptic neurotransmission in the hippocampus. We recorded the slope of fEPSPs in CA1 by stimulating the Schaffer collaterals in 4-month-old BDNF$^{Met/Met}$ mice and matched wild-type mice. The input–output relationship of fEPSP slope in BDNF$^{Met/Met}$ mice and wild-type mice were not statistically different (Fig. 1*A*) (two-way ANOVA, $p > 0.05$). These results suggest that the BDNF Val66Met polymorphism does not markedly affect basal synaptic neurotransmission at the CA3–CA1 synapses.

Next, we examined PPF, a short-term plasticity that reflect a presynaptic mechanism (Hess et al., 1987; Zucker, 1989; Chen et al., 2004). The PPF in BDNF$^{Met/Met}$ mice and wild-type mice was not statistically different, suggesting that the BDNF Val66Met

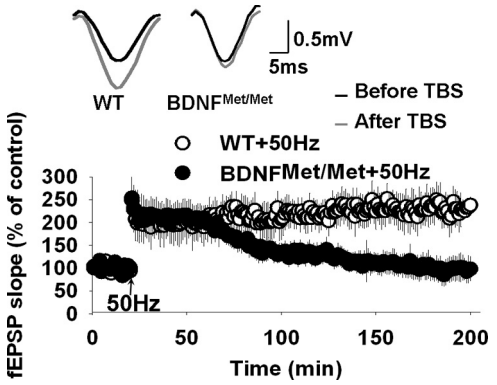

Figure 2. BDNF$^{Met/Met}$ mice exhibit an altered NMDA receptor-dependent postsynaptic LTP at the CA3–CA1 synapses. The graph shows 50 Hz-induced LTP at the CA3–CA1 synapses of 4-month-old BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). BDNF$^{Met/Met}$ and wild-type groups that did not receive the 50 Hz stimulation showed stable fEPSP slope during the course of recording. Inset, Examples of fEPSP recordings before 50 Hz stimulation and at 180 min after 50 Hz stimulation.

polymorphism did not affect presynaptic release probability at the CA3–CA1 synapses (Fig. 1*B*) (two-way ANOVA, $p > 0.05$). Consistently, we did not find any significant difference in either frequency or amplitude of mEPSCs recorded from the CA1 pyramidal neurons of BDNF$^{Met/Met}$ and matched wild-type mice (Fig. 1*C–E*).

To examine activity-dependent synaptic plasticity in BDNF$^{Met/Met}$ mice, we compared the effect of theta-burst stimulation (TBS) on LTP in BDNF$^{Met/Met}$ and wild-type mice. TBS-induced LTP requires activation of NMDA receptors and is believed to involve both presynaptic and postsynaptic mechanisms (Malinow, 1991; Malenka and Nicoll, 1999; Morgan and Teyler, 2001; Zakharenko et al., 2001, 2003). Although the application of TBS produced robust LTP in 1-month-old wild-type mice, LTP in BDNF$^{Met/Met}$ mice was virtually absent (Fig. 1*F*) ($F_{(1,13)} = 8.44$, two-way ANOVA, $p < 0.01$). These results suggest that the BDNF Val66Met polymorphism affected LTP in the hippocampus. We also examined TBS-induced LTP in 4-month-old BDNF$^{Met/Met}$ and age-matched wild-type mice. In these older animals, the BDNF$^{Met/Met}$ mice showed an early TBS-induced potentiation that declined to baseline within 2 h. Similar to the LTP in 1-month-old mice, however, we observed significantly lower levels of late LTP in BDNF$^{Met/Met}$ mice compared to the wild-type mice (Fig. 1*G*) ($F_{(1,14)} = 5.9$, two-way ANOVA, $p < 0.01$). BDNF$^{Met/Met}$ and wild-type groups that did not receive TBS showed stable fEPSP slope during the course of recording (data not shown).

To study the effect of BDNF Val66Met polymorphism on LTP further, we compared the effect of 50 Hz stimulation (three 1 s trains of 50 Hz stimulation applied every 20 s)-induced LTP in 4-month-old BDNF$^{Met/Met}$ mice and wild-type mice. Similar to the LTP induced by TBS, 50 Hz-induced LTP in BDNF$^{Met/Met}$ mice was significantly lower than that in wild-type mice (Fig. 2) ($F_{(1,14)} = 5.3$, two-way ANOVA, $p < 0.01$). BDNF$^{Met/Met}$ and wild-type groups that did not receive the 50 Hz stimulation showed stable fEPSP slope during the course of recording (data not shown). This 50 Hz protocol has been reported to induce NMDA receptor-dependent postsynaptic LTP at the CA3–CA1 synapses (Zakharenko et al., 2001, 2003). The results described above confirm that the BDNF Val66Met polymorphism causes a major reduction in hippocampal LTP.

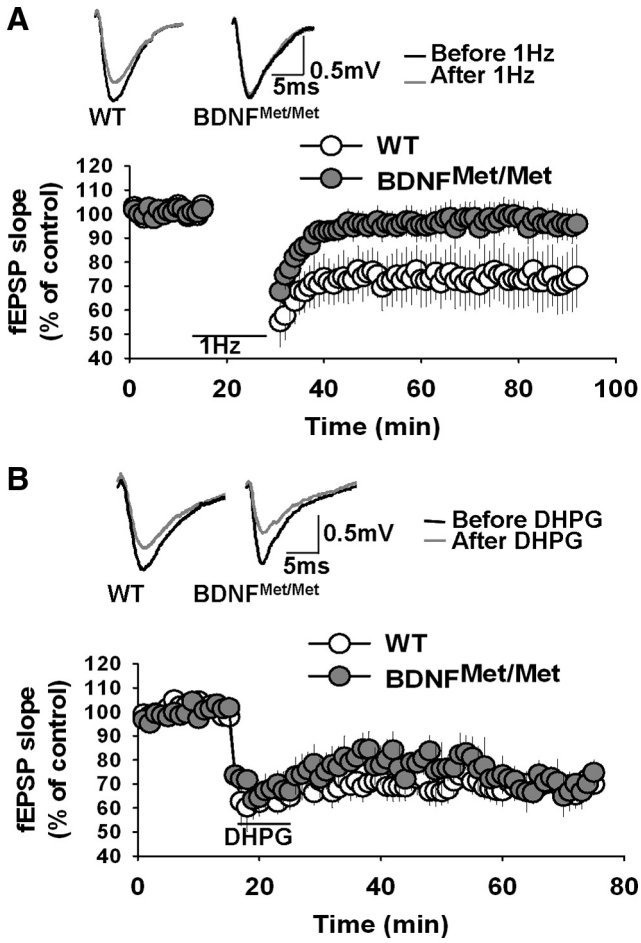

Figure 3. The BDNF Val66Met polymorphism interferes with NMDA receptor-dependent LTD but not mGluR-dependent LTD. ***A***, Low-frequency stimulation (1 Hz)-induced LTD at the CA3–CA1 synapses of 1-month-old BDNF$^{Met/Met}$ ($n = 7$) and matched wild-type mice ($n = 9$). ***B***, DHPG-induced LTD at the CA3–CA1 synapses of 1-month-old BDNF$^{Met/Met}$ ($n = 7$) and matched wild-type mice ($n = 7$). Inset, Examples of fEPSP recordings before 1 Hz stimulation/DHPG application and at 60 min after 1 Hz stimulation/DHPG application.

The BDNF Val66Met polymorphism selectively interferes with NMDA receptor-dependent LTD

Similar to the purported role of LTP in hippocampus-dependent cognitive functions, LTD is also believed to play a role in hippocampal functions (Bear and Abraham, 1996). To examine whether the BDNF Val66Met polymorphism has any effect upon LTD at the CA3–CA1 synapses, we used an established induction protocol for NMDA receptor-dependent LTD, application of 900 pulses at 1 Hz (Massey and Bashir, 2007). Application of 1 Hz stimulation produced reliable LTD in 1-month-old wild-type mice (Fig. 3*A*) (repeated-measures ANOVA, $p < 0.01$). However, LTD in BDNF$^{Met/Met}$ slices was significantly lower than that in the wild-type slices (Fig. 3*A*) ($F_{(1,15)} = 6.42$, two-way ANOVA, $p < 0.01$). These results suggested that the BDNF Val66Met polymorphism affected not only LTP, but also LTD at the CA3–CA1 synapse.

To examine whether the effect of the BDNF Val66Met polymorphism was selective for NMDA receptor-dependent LTD, we studied mGluR-dependent LTD in BDNF$^{Met/Met}$ mice. Application of mGluR agonist DHPG normally induces LTD at the CA3–CA1 synapse in young animals in an NMDA receptor-independent fashion (Fitzjohn et al., 1999; Kumar and Foster, 2007). Application of 100 μM DHPG for 10 min induced reliable LTD in the wild-type mice as

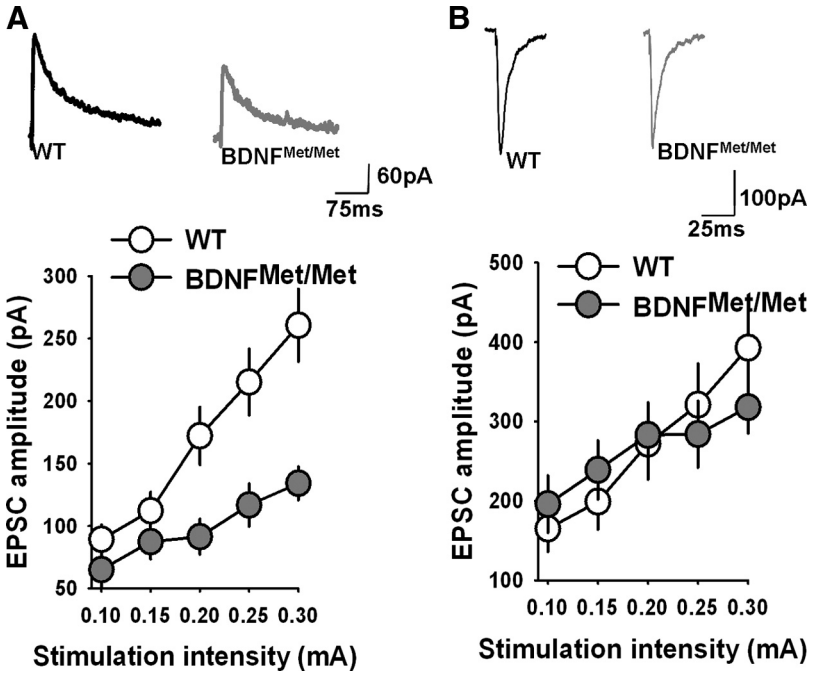

Figure 4. BDNF$^{Met/Met}$ mice exhibit reduced NMDA receptor neurotransmission but normal non-NMDA receptor neurotransmission in the CA1 pyramidal neurons. ***A***, Average NMDA EPSC amplitude in the CA1 pyramidal neurons of BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). ***B***, Average non-NMDA EPSC amplitude in the CA1 pyramidal neurons of BDNF$^{Met/Met}$ ($n = 8$) and matched wild-type mice ($n = 8$). Inset, Examples of EPSC recordings.

reported previously (Fig. 3*B*) (repeated-measures ANOVA, $p < 0.01$) (Kumar and Foster, 2007). Interestingly, DHPG-induced LTD in BDNF$^{Met/Met}$ mice was not significantly different from wild-type mice (Fig. 3*B*) (two-way ANOVA, $p > 0.05$). Thus, the BDNF Val66Met polymorphism selectively reduces NMDA receptor-dependent LTD but not the mGluR-dependent LTD at the hippocampal CA3–CA1 synapses.

BDNF$^{Met/Met}$ mice exhibit reduced NMDA receptor neurotransmission in the CA1 pyramidal neurons

The aforementioned LTP and LTD experiments strongly suggested that the BDNF Val66Met polymorphism affects NMDA receptor-dependent synaptic plasticity at the CA3–CA1 synapses. Therefore, it is possible that the BDNF Val66Met polymorphism alters NMDA receptor neurotransmission at the CA3–CA1 synapses. To determine whether NMDA receptor neurotransmission is modified at the CA3–CA1 synapses of BDNF$^{Met/Met}$ mice, we measured NMDA EPSC amplitude in the CA1 pyramidal neurons by whole-cell recording at +40 mV in the presence of bicuculline (to block $GABA_A$ receptors) and NBQX (to block AMPA receptors) by stimulation of the Schaffer collaterals. The average amplitudes of NMDA EPSCs in BDNF$^{Met/Met}$ mice were significantly lower than those observed in wild-type mice (Fig. 4*A*) ($F_{(1,14)} = 11.2$, two-way ANOVA, $p < 0.01$), suggesting reduced NMDA receptor neurotransmission in the CA1 pyramidal neurons of BDNF$^{Met/Met}$ mice. The input–output analysis of fEPSPs indicated that the BDNF Val66Met polymorphism did not affect non-NMDA receptor neurotransmission at the CA3–CA1 synapses (Fig. 1*A*). EPSCs evoked at −60 mV in the presence of bicuculline and D-APV (to block NMDA receptors) in BDNF$^{Met/Met}$ mice were not significantly different from age-matched wild-type animals, suggesting that non-NMDA receptor neurotransmission is normal in the CA1 pyramidal neurons of BDNF$^{Met/Met}$ mice (Fig. 4*B*) (two-way ANOVA, $p > 0.05$). The lack of evidence for modification of non-NMDA receptor neurotransmission further supports an NMDA receptor-specific impairment of synaptic functions in BDNF$^{Met/Met}$ mice.

Discussion

Recent human and animal studies have suggested a role for the BDNF Val66Met polymorphism in hippocampus-dependent cognitive functions (Egan et al., 2003; Hariri et al., 2003; Chen et al., 2006). Therefore, we examined whether and how the BDNF Val66Met polymorphism affects hippocampal neurotransmission and synaptic plasticity using BDNF$^{Met/Met}$ mice. Both young and adult BDNF$^{Met/Met}$ mice exhibited a decrease in TBS-induced LTP at the CA3–CA1 synapses. Earlier studies demonstrated that TBS-induced LTP required activation of NMDA receptors and involved both presynaptic and postsynaptic mechanisms (Malinow, 1991; Malenka and Nicoll, 1999; Morgan and Teyler, 2001; Zakharenko et al., 2001, 2003). Also, BDNF release was involved in TBS-induced LTP (Patterson et al., 2001; Zakharenko et al., 2003). Results from our experiments using a postsynaptic LTP induced by 50 Hz stimulation revealed that this form of LTP is also impaired in BDNF$^{Met/Met}$ mice. An earlier study in CA3–CA1 restricted BDNF knock-out mice showed normal 50 Hz-induced LTP (Zakharenko et al., 2003). In contrast, unrestricted BDNF knock-out mice showed impairment of 100 Hz-induced LTP, an experimental protocol similar to 50 Hz-induced LTP (Korte et al., 1995, 1996; Patterson et al., 1996). Therefore, it is possible that the difference in 50 Hz-induced LTP in BDNF$^{Met/Met}$ mice and CA3–CA1 restricted BDNF knock-out mice is due to the global reduction of BDNF signaling in BDNF$^{Met/Met}$ mice (Zakharenko et al., 2003).

Consistent with a reduction in NMDA receptor-dependent LTP in BDNF$^{Met/Met}$ mice, we also observed a decrease in NMDA receptor-dependent LTD in these mice. A postsynaptic increase in calcium through NMDA receptors is critical for the induction of low-frequency stimulation-induced LTD (Malenka and Bear, 2004). Endocytosis of the GluR2 subunit of AMPA receptors in response to activation of NMDA receptors is believed to be involved in low-frequency stimulation-induced LTD (Lee et al., 2002; Malenka and Bear, 2004). The effect of BDNF Val66Met polymorphism on LTD is specific, since mGluR-dependent LTD was unaffected in BDNF$^{Met/Met}$ mice. LTD in the hippocampus can be mediated by the activation of group 1 mGluR receptors, which is dependent upon an elevation of intracellular calcium and is independent of NMDA receptor activation (Kemp and Bashir, 2001; Gladding et al., 2009). Earlier studies showed group 1 mGluR receptor-initiated LTD in a clathrin-dependent manner postsynaptically (Xiao et al., 2001). The selective reduction of NMDA receptor-dependent LTD, and not mGluR-dependent LTD, suggests that the BDNF Val66Met polymorphism has a specific effect on hippocampal plasticity.

The molecular pathway by which BDNF modulates NMDA receptor function is not clearly understood. BDNF can enhance phosphorylation of NMDA receptors and NMDA receptor activity (Suen et al., 1997; Levine et al., 1998; Lin et al., 1998; Crozier et al., 2008). Also, BDNF can regulate trafficking and expression of

NMDA receptors (Caldeira et al., 2007). It is possible that the BDNF Val66Met polymorphism affects aforementioned regulation of NMDA receptor functions resulting in impaired synaptic plasticity. However, we cannot rule out the potential role of acute activity-dependent release of BDNF in altered synaptic plasticity in BDNF$^{Met/Met}$ mice. Future studies will be necessary to investigate the effect of the BDNF Val66Met polymorphism on synapse-specific release of BDNF and its direct role in synaptic plasticity.

In conclusion, the present study demonstrates that the BDNF Val66Met polymorphism has functional consequences in NMDA receptor neurotransmission and synaptic plasticity in the hippocampus. Alterations in hippocampal synaptic function are likely to play a role in cognitive deficits associated with the BDNF Val66Met polymorphism.

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