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Journal

Journal of Neuroscience, 30(43)

ISSN

1529-2401

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Publication Date

2010-10-27

Peer reviewed

Published in final edited form as:

J Neurosci. 2010 October 27; 30(43): 14440–14445. doi:10.1523/JNEUROSCI.3310-10.2010.

Presynaptic BDNF Promotes Post-Synaptic Long-Term Potentiation in the Dorsal Striatum

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Abstract

Brain-Derived Neurotrophic Factor (BDNF) facilitates the formation of long-term potentiation (LTP) in hippocampus but whether this involves release from pre- vs. post-synaptic pools is unclear. We therefore tested if BDNF is essential for LTP in dorsal striatum, a structure in which the neurotrophin is present only in afferent terminals. Whole cell recordings were collected from medium spiny neurons in striatal slices prepared from adult mice. High frequency stimulation (HFS) of neocortical afferents produced a rapid and stable NMDA receptor-dependent potentiation. The ratio of AMPA to NMDA receptor-mediated components of the EPSPs was substantially increased after inducing potentiation, suggesting that potentiation involved post-synaptic changes. In accord with this, paired pulse response ratios, a measure of transmitter release kinetics, were reduced by elevated calcium but not by LTP. Infusion of the BDNF scavenger TrkB-Fc blocked the formation of potentiation, beginning with the second minute post-HFS, without reducing responses to HFS. These results suggest that presynaptic pools of BDNF can act within 2 minutes of HFS to support the formation of a post-synaptic form of LTP in striatum.

Keywords

synaptic plasticity; caudate; medium spiny neuron; TrkB; neurotrophin; NMDA receptor

Introduction

Results of electrophysiological studies using neutralizing antisera, genetic manipulation or chimeric ligand-scavenger proteins (Korte et al., 1998; Minichiello, 2009) indicate that endogenous BDNF, acting through its TrkB receptor, positively modulates processes leading to stable LTP in hippocampus. How the neurotrophin produces these effects has been the subject of considerable research. BDNF can enhance neurotransmitter release during trains of afferent stimulation (Figurov et al., 1996; Gottschalk et al., 1998), but there is also evidence that it facilitates the post-synaptic signaling, calcium modulation (Kovalchuk et al., 2002) and cytoskeletal remodeling (Messaoudi et al., 2007; Rex et al., 2007) required for the production of stable potentiation. BDNF's contribution to these events thus provides a likely explanation for its potent influence on LTP.

The location of the BDNF pool most pertinent to LTP has not been determined. BDNF is anterogradely transported to both axon terminals (Goodman et al., 1996; Altar and

DiStefano, 1998; Conner et al., 1998; Haubensak et al., 1998) and dendritic arbors (Adachi et al., 2005; Matsuda et al., 2009) and is released from cultured neurons by high frequency or theta burst stimulation (TBS) (Balkowiec and Katz, 2002; Gartner and Staiger, 2002). TBS reportedly increases local, extracellular concentrations of BDNF for about 10 minutes in brain slices (Aicardi et al., 2004). Cultured neuron studies have shown that depolarization, afferent stimulation, and back-propagating action potentials elicit BDNF release from dendrites (Kuczewski et al., 2008; Lessmann and Brigadski, 2009) with lesser depletion of vesicular BDNF from axons (Matsuda et al., 2009). Thus, the induction of LTP may cause dendritic BDNF release followed by autocrine signaling through post-synaptic TrkB receptors. However, the relative contributions of secretion from axonal vs. dendritic compartments to LTP has not been evaluated for adult neurons expressing native BDNF in situ.

The present studies investigated the potential role of presynaptic BDNF pools in LTP using the cortico-striatal projection system. The medium spiny cells that comprise the great majority of neurons in striatum do not express BDNF at detectable levels (Conner et al., 1997; Fumagalli et al., 2007) and the sizable concentrations of BDNF in the structure are largely located within cortical afferents (Altar et al., 1997). The cortico-striatal system is thus particularly appropriate for testing if pre-synaptic BDNF supports the production of LTP.

Materials and Methods

Animals were anaesthetized with fluorothane and killed by decapitation in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with protocols approved by the Institutional Animal Care and Use Committee of the University of California at Irvine.

Slice preparation

Parahorizontal cortico-striatal slices (270 μ m thick) were prepared from 2 mo old male CB57BL/6J mice using a Leica Vibroslicer and maintained at 30-32°C for ≥ 1 hour in artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 3 KCl, 1.25 KH_2PO_4 , 3.4 CaCl_2 , 2.5 MgSO_4 , 26 NaHCO_3 , and 10 D-glucose, pH 7.3 and oxygenated with 95% O_2 and 5% CO_2 .

Electrophysiological recordings

Slices were placed in a recording chamber, submerged, and continuously perfused at 2-3 ml/min with oxygenated modified ACSF (0mM Mg^{++} , 5mM Ca^{++}) at 32°C unless otherwise indicated. Whole cell current-clamp recordings were made with an Axopatch 200A amplifier (Molecular Devices). Data were filtered at 2 kHz, digitized at 1-5 kHz, stored on a computer and analyzed off-line using Mini Analysis Program (Synaptosoft), Origin (OriginLab), and pCLAMP 7 (Axon Instruments). Medium-sized spiny neurons (MSN) in dorsolateral striatum were visualized using an 60X water-immersion objective and infrared differential interference optics video microscopy, and identified by morphology (small somata, post hoc analysis of Neurobiotin or AlexaFluor488 filling revealed multiple primary dendrites with a high spine density in their oblique branches). MSN were additionally identified by their intrinsic membrane properties (e.g., resting membrane potential typically more negative than -80 mV, inward and outward rectification in response to somatic current injection, a long depolarizing ramp to the AP threshold leading to a delayed spike discharge) (Kawaguchi et al., 1989). Borosilicate glass patch electrodes had a resistance of 3-8 M Ω after being filled with pipette solution 1 (130 K gluconate, 10 KCl, 0.2 EGTA, 8 NaCl, 2

ATP, 0.3 GTP, and 10 HEPES, pH 7.35, 290–300 mOsm). For voltage-clamp recordings, K gluconate was replaced by cesium methane-sulfonate.

For most experiments, cells were filled with Neurobiotin (Vector Labs) or AlexaFluor 488 (Invitrogen) (3 mg/ml or 60 μ g/ml in the patch-clamp pipette, respectively) during recordings. Neurobiotin was visualized as described (Brunson et al., 2005). For AlexaFluor 488 fills, slice whole mounts were viewed using epifluorescence illumination.

Cortico-striatal pathway stimulation

Responses were evoked in MSNs by extracellular stimulation (0.01 ms, 0.05 Hz) with bipolar electrodes (FHC) placed in cortical layer VI close to the white matter. Recordings were rejected if the initial V_m was more positive than -78 mV or if V_m changed by ≥ 10 % and input resistance changed by ≥ 30 % during recordings. After 10 min of recording stable responses, high frequency stimulation (HFS) (four 1 sec, 100 Hz trains at 10 sec intervals) was delivered. The relative EPSP change was determined by comparing the normalized mean response from 25 to 30 min post-HFS with the mean EPSP over the 10-min immediately prior to HFS. The criterion used to determine the induction of LTP was a 20% increase in evoked responses relative to baseline as assessed from normalized values. Data are expressed as means $\pm$ SEM and Student's *t* test was used for statistical analysis, unless otherwise stated.

For comparisons of treatment effects on EPSP amplitude between slices, the values of each recording were normalized to the average amplitude for the 10 min of baseline before a compound was added. To quantify effects of compounds on EPSP amplitude, values from the last 3 min of compound application were averaged for each slice. Differences were considered significant when $p < 0.05$.

Receptor antagonists

For all experiments, 50 μ M picrotoxin (GABA_A receptor blocker) was added to the ACSF. Where indicated, the AMPA receptor (AMPA) antagonist CNQX (20 μ M) or the NMDA receptor (NMDAR) antagonist D-2-amino-5-phosphonopentanoic acid (APV; 50 μ M) was added as well. Data for APV experiments were used only if responses decreased by ≥ 20 % within 4 min of infusion onset and remained depressed below that level.

Results

Previous work showed that LTP is more difficult to elicit in cortico-striatal than in hippocampal slice preparations across stimulation protocols (e.g., spike timing (Shen et al, 2008), multiple trains, post-synaptic depolarization, etc) but can be obtained in low magnesium/high calcium medium (Calabresi et al., 2007; Lovinger 2010). Pilot experiments confirmed the latter point and we conducted most of the following studies under these conditions. Recordings were made from medium spiny neurons (MSNs), which were recognizable by morphological features and by a characteristic inward rectification (Fig 1A). Neurons were also filled with Neurobiotin or AlexaFluor 488 for subsequent morphological confirmation (Fig 1B). EPSPs, recorded in the presence of the GABA-A receptor antagonist picrotoxin, were comparable to those described in the literature (Rohrbacher et al., 1994; Moriguchi et al., 2002; Li et al., 2009) and were notable for having a slow decay constant. Previous studies have described a significant NMDAR-mediated component to EPSPs recorded from MSNs (Li et al., 2009) and, in agreement with this, we found that the AMPAR antagonist CNQX reduced the amplitude of cortically evoked responses by almost half; the remainder of the fast response was eliminated by the NMDAR antagonist APV (Fig 1C).

High frequency stimulation (HFS) trains, in accord with previous reports (Partridge et al., 2000; Fino et al., 2005; Marrone et al., 2006; Li et al., 2009), did not trigger lasting potentiation of striatal EPSPs when administered in the presence of APV (Fig 2A), indicating that NMDARs are necessary for induction but by themselves do not express LTP. As noted, APV substantially reduced pre-HFS baseline responses. We further investigated the pre- vs. post-synaptic locus of potentiation by comparing effects of APV on potentiated responses with those on baseline EPSPs. HFS caused a marked and stable potentiation effect that was only partially reduced by APV infusion (Fig 2B). Direct comparison of APV's effects on baseline vs. potentiated responses indicated that the antagonist had smaller effects on the latter: the percent reduction for baseline EPSPs was $43.2 \pm 7.0\%$ (mean $\pm$ SD) whereas that for potentiated EPSPs was $34.6 \pm 3.6\%$ ($p=0.022$; t-test with Welch correction, 2-tails). The differential effect of APV strongly suggests that much of the potentiation involved selective enhancement of AMPAR-gated currents.

We further tested the above conclusion by comparing paired pulse response ratios (PPRs), a measure sensitive to release probability, for the cortico-striatal EPSCs before and after induction of LTP. Slices were perfused with 2mM Ca^{++} /2mM Mg^{++} containing ACSF, switched to 5mM Ca^{++} /0mM Mg^{++} for 5 min for induction of LTP, and then returned to 2mM Ca^{++} /2mM Mg^{++} . Twin pulses separated by 50 msec were delivered throughout the analysis. Two of six cells exhibited paired pulse facilitation (30%) while the remainder did not, in agreement with reports of variable PPRs at cortico-striatal synapses (Cepeda et al., 2008). The switch to high calcium caused an evident increase in EPSCs (Fig 2C); HFS delivered at the end of high calcium infusion induced robust potentiation that remained in place following the return to low calcium medium. The increase in EPSC amplitudes recorded at the end of the 5 min high calcium / low magnesium treatment ($38.2 \pm 12\%$) was accompanied by a reliable decrease in PPR ($16.7 \pm 5\%$; $p<0.01$, paired t-test, 2 tails), as expected for a measure sensitive to release kinetics (Fig 2D, "high Ca^{++} "). The experimental question was whether the increase in synaptic responses that constitutes striatal LTP would similarly reduce PPR. This was not the case: a $78.1 \pm 21.9\%$ increase (measured 25-35 min post-HFS) in EPSC amplitude above baseline was not accompanied by a change in PPR (-1.9 ± 6.9 , $p=0.60$) (Fig 2D, "HFS").

Having found that LTP at cortico-striatal synapses shares several features with hippocampal potentiation (i.e., predominant changes in AMPAR-mediated responses; little to no change in PPR) (Kauer et al., 1988; Muller et al., 1988; Muller and Lynch, 1988), we tested if it has similar dependency upon BDNF. The extracellular BDNF scavenger TrkB-Fc, applied at concentrations shown to block cell signaling changes induced by BDNF (Rex et al., 2007), had no evident effects on baseline responses during a 45-minute infusion. This agrees with effects in hippocampus (Kovalchuk et al., 2002; Rex et al., 2007). TrkB-Fc did, however, produce a striking suppression of cortico-striatal LTP. HFS delivered to control slices produced stable response facilitation, as described; the same stimulation administered in the presence of TrkB-Fc caused transient facilitation that dissipated within the first one to two minutes post-induction (Fig 3A, left). We quantified this unexpectedly rapid and complete effect of the scavenger by averaging responses for each of the first 10 minutes post-induction. As shown in Figure 3A (right), the response facilitation produced by HFS was undetectable by the second minute post-induction. Differences in percent potentiation between control and experimental slices were highly significant ($p<0.0001$ for 2-10 min post-HFS). Comparable effects were obtained with the tyrosine kinase inhibitor K252a that blocks Trk autophosphorylation and signaling (Knusel and Hefti, 1992) (Supplemental Fig. 1). Comparisons between these results and those described for the hippocampus suggest that BDNF has a substantially greater effect on synaptic plasticity in striatum.

We next tested if the potent effects of TrkB-Fc were due to actions on responses to HFS. The accumulated depolarization to the 1 sec trains of HFS was not different in control vs. TrkB-Fc treated slices (Fig 3B, left); measurements indicated that the peak response amplitudes, and the within-train time to peak, were comparable for control and scavenger-treated slices (Fig 3B, right). The possibility remains that the NMDAR component of the HFS response is enhanced to a degree that promotes potentiation but is too small to be detected in the composite responses. We investigated this by asking if BDNF affects NMDAR-dependent EPSPs in striatum. The results were clear: 30-min infusion of BDNF in the presence of the AMPAR antagonist CNQX increased pharmacologically isolated NMDAR responses ($45 \pm 12\%$; Fig 3C, bottom traces).

These results led us to ask if scavenging extracellular BDNF reduces NMDAR-gated responses to HFS. We tested this by applying an HFS train to a cell during perfusion of CNQX and then repeating it 10 min later in the presence of vehicle or TrkB-Fc. Surprisingly, given the results for infused BDNF, TrkB-Fc did not reduce the composite inward currents mediated by NMDARs during a one second HFS train (Fig 3D, left). Quantitative measures across multiple slices gave no indication that NMDAR-mediated burst responses were reduced in their amplitudes or times to peak amplitude by TrkB-Fc (Fig 3D, right). It follows from this that BDNF's contributions to LTP occur at some point after induction.

Discussion

LTP was more difficult to elicit in cortico-striatal projections than is the case for intra-hippocampal pathways. We found it necessary to use high frequency stimulation trains and GABA receptor antagonists to reliably obtain potentiation in striatum whereas only 4 or 5 theta bursts are needed to trigger robust LTP in hippocampal slices. It is thus not surprising that various groups have reported that LTP is poorly developed in striatum (Calabresi et al., 2007). The high threshold for the induction of potentiation could reflect the absence of positive modulators rather than being an indication that LTP-type plasticity is only rarely employed within the basal ganglia. Dopamine, the absence of which impairs LTP in the striatum (Centonze et al., 1999; Pawlak and Kerr, 2008; Schotanus and Chergui, 2008), is an obvious candidate for an under-represented plasticity factor in our experiments. It should be noted, however, that there appear to be no reports showing that enhancing dopaminergic transmission lowers the threshold for striatal LTP. Testing this point is a reasonable first step in asking if plasticity in the striatum occurs with a much lower probability than is the case for the cortical telencephalon.

Despite its elevated threshold, we found striatal LTP possessed a number of features that characterize potentiation in hippocampus. It is synapse-specific, not accompanied by evident changes in release kinetics as assessed by PPRs, and requires NMDAR activation for induction. We also obtained evidence that cortico-striatal potentiation is expressed by changes in AMPARs to a greater degree than NMDARs. EPSPs in striatum, in contrast to those in hippocampus, contain a sizable NMDAR-mediated component. This made it possible to carry out reasonably direct comparisons of the contributions of AMPA vs. NMDA receptors to cortico-striatal responses prior to and following induction of LTP. The percent of the EPSP contributed by NMDARs, as estimated from the depression produced by APV, was significantly reduced at potentiated synapses. This result accords with measurements made of hippocampal LTP (Kauer et al., 1988; Muller and Lynch, 1988; Manabe and Nicoll, 1994) in showing that the AMPAR-mediated component of the synaptic response is differentially elevated by potentiation. Findings in both regions indicate that LTP reflects post-synaptic mechanisms as opposed to changes in presynaptic glutamate release, which would be predicted to influence AMPA and NMDA receptor-mediated responses to a

comparable extent. The absence of changes to paired pulse ratios, a measure sensitive to conditions that affect release probability (elevated ACSF calcium levels), following induction of LTP also argues against a quantitatively meaningful pre-synaptic contribution to cortico-striatal potentiation.

The present findings constitute the first evidence that activity-induced LTP outside the cortical telencephalon is dependent upon BDNF. Infusion of the ligand scavenger TrkB-Fc completely blocked LTP of cortico-striatal synapses as did the Trk signaling antagonist K252a, indicating that endogenous BDNF plays a potent and essential role in generating stable potentiation. The scavenger eliminated response enhancement by the second minute after HFS, indicating that BDNF acts on very early phases of potentiation in striatum. The mechanisms through which BDNF promotes LTP of cortico-striatal synapses remain to be studied but our results suggest that post-induction processes are involved. TrkB-Fc had little or no effect on baseline EPSPs or the composite response to HFS. Thirty minute BDNF infusions enhanced NMDAR-mediated EPSPs but TrkB-Fc did not reduce the isolated NMDAR-mediated responses to HFS. Thus, it seems that prolonged exposures to infused BDNF initiate changes that are not triggered by the much briefer release events occurring during HFS. In any event, the absence of a TrkB-Fc effect on baseline and burst responses strongly suggests that endogenous BDNF promotes potentiation by transiently engaging post-synaptic mechanisms such as the signaling to actin shown to be critical for hippocampal LTP (Lynch et al., 2008; Rex et al., 2009).

The present results demonstrate that, for this particular system, release of pre-synaptic BDNF is fully capable of promoting the post-synaptic events responsible for the induction and expression of LTP. Although the locus of the LTP-related pools within hippocampus remain to be determined, multiple studies have shown that BDNF in striatum is predominantly contained within cortico-striatal afferents as opposed to resident neurons (Altar et al., 1997; Conner et al., 1997; Fumagalli et al., 2007). Thus, there is little ambiguity regarding the origins of local extracellular BDNF contributing to striatal LTP. It remains now to isolate the mechanisms underlying neurotrophin release from cortical terminals in striatum. Evidence that such systems are required for LTP at various sites in cortical telencephalon would constitute strong evidence that conjoint release of glutamate and BDNF from terminals is a ubiquitous requirement for the potentiation effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NINDS grant NS045260 to GL and CMG. The authors thank M. Jafari and Dr. J.C. Lauterborn for assistance with photomicroscopy, and Dr. M.S. Levine (UCLA) for valuable advice and discussions.

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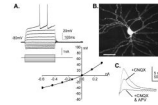


Figure 1. Characteristics of striatal neurons

A) Whole cell recordings indicate that the neurons have a resting membrane potential of about -80mV and emit scattered spikes at about -40mV . The input /output curve is indicative of inward rectification. B) Intracellular fills with AlexaFluor 488 confirm that the recorded cells are medium spiny neurons (Bar= $30\mu\text{m}$). C) EPSPs elicited by cortical stimulation are partially blocked by CNQX; subsequent perfusion of APV eliminates nearly all of the remaining response.

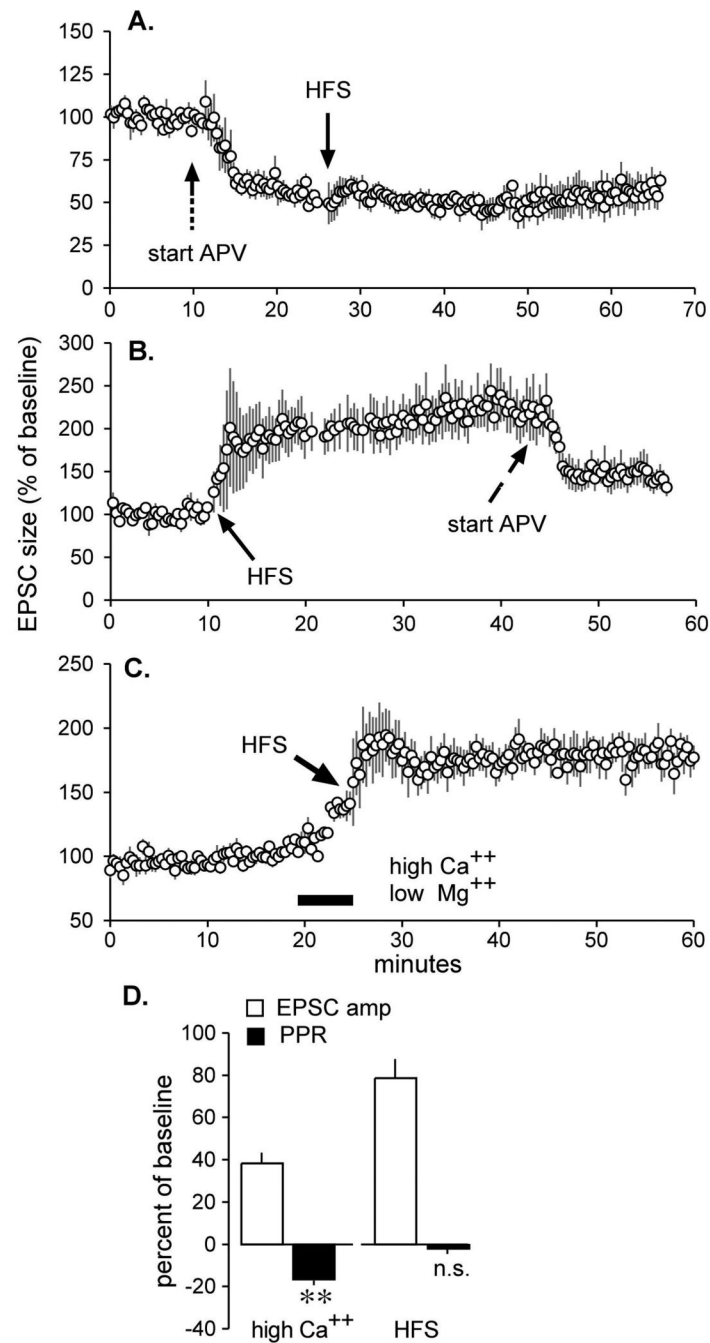


Figure 2. Induction of LTP reduced the NMDAR-mediated component of synaptic responses but did not affect paired pulse ratios

A) APV infused continuously prior to the delivery of high frequency stimulation (HFS) blocked induction of LTP. B) Effects of APV when infused after HFS and the induction of LTP. C) Baseline measurements and magnitude of LTP were recorded in slices perfused with ACSF containing 2mM Ca^{++} and 2mM Mg^{++} ; HFS delivered at the end of 5 min infusion of 5mM Ca^{++} and 0mM Mg^{++} (black bar) produced potentiation that remained in place when lower calcium conditions were restored. D) Five minutes of high calcium increased the EPSC amplitude (amp) and reliably reduced the paired pulse ratio (PPR) (** $p < 0.01$). Applied at the end of high calcium infusion, HFS further increased the EPSC

amplitude without measurably affecting the PPR (n.s. denotes $p > 0.05$ vs baseline). Plots show means $\pm$ SEM for 5-7 slices/group.

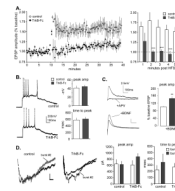


Figure 3. TrkB-Fc blocks LTP without changing responses to HFS

A) [Left] HFS caused a long lasting increase in EPSP amplitude under control conditions but not when delivered in the presence of TrkB-Fc. [Right] Effects of TrkB-Fc were evident shortly after HFS: plot shows that averaged responses for post-HFS minutes 2-10 were not elevated above baseline (dashed line) and were reduced relative to potentiated values found in control slices ($***p < 0.001$ for 2-10 min post-HFS). B) Composite responses to 1 sec HFS were comparable for control and TrkB-Fc-treated slices. Typical responses are shown at left; peak amplitudes and times-to-peak are summarized on the right. C) Infused BDNF increased the size of the isolated NMDAR component of the EPSP. The upper traces show that the tested responses were completely blocked by APV; lower traces illustrate the effects of BDNF. Bar graph summarizes the group effect of BDNF treatment ($**p < 0.01$). D) [Left] Representative traces of isolated (CNQX present) NMDAR-mediated responses to one second HFS trains delivered prior to (burst #1) and 10 min after (burst #2) infusion of vehicle ('control') or TrkB-Fc (scale bars: 100pA; 100msec). [Right] Bar graphs show peak amplitudes and time-to-peak for the composite responses to the first and second HFS trains for control and TrkB-Fc-treated slices. Note that TrkB-Fc infusion did not reduce either variable. Plots show mean $\pm$ SEM values for 6-8 slices/group.