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Brain-derived neurotrophic factor alters the synaptic modification threshold in visual cortex

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Abstract

The effects of brain-derived neurotrophic factor (BDNF) were investigated on synaptic transmission and two forms of activity-dependent synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), in visual cortex slices prepared from young (P21–28) rats. The slices treated for 2–5 h in BDNF showed no difference from control slices when a 'strong' tetanus was used (theta-burst stimulation) to elicit a maximal level of LTP but displayed significantly greater synaptic potentiation in response to a 'weak' (20 Hz) tetanus. The BDNF-treated slices also showed significantly less LTD in response to a 1 Hz tetanus. Thus, BDNF treatment alters the relationship between stimulation frequency and synaptic plasticity in the visual cortex, shifting the modification threshold to the left. The effects of BDNF on LTP and LTD induction may be attributed to the significant enhancement of synaptic responses that was observed during conditioning stimulation. These data suggest that one role of BDNF during development of the visual cortex may be to modulate the properties of synaptic plasticity, enhancing synaptic strengthening and reducing synaptic weakening processes which contribute to the formation of specific synaptic connections.

Keywords: Neurotrophin; Long-term potentiation; Long-term depression; Visual cortical plasticity

There is now considerable evidence that neurotrophins, particularly brain-derived neurotrophic factor (BDNF), play diverse roles in regulating the organization of visual cortex at different stages of development (Bonhoeffer, 1996; Cellerino and Maffei, 1996; Katz and Shatz, 1996). During fetal development, BDNF is crucial for neuronal survival (Ghosh et al., 1994). It interacts with activity during the perinatal period to regulate neuronal differentiation (McAllister et al., 1996, 1997) and in the postnatal period BDNF regulates the activity-dependent plasticity of cortical synapses (Cabelli et al., 1995; Galuske et al., 1996; Cabelli et al., 1997).

An interesting example of BDNF modulation of visual cortical synaptic plasticity comes from the work of Cabelli et al. (1995). They found that intracortical infusion of BDNF disrupts the normal segregation of geniculocortical axons into ocular dominance columns. The process of ocular dominance column formation reflects the activity-dependent competition of axons synapsing on common postsynaptic targets (Katz and Shatz, 1996). If the synapses normally compete for the trophic support provided by a limited supply of postsynaptically released BDNF, then application of exogenous neurotrophin might support the axons that usually would be withdrawn, thus preventing ocular dominance column segregation.

An alternative to the neurotrophin-competition hypothesis is a model in which competition occurs initially via the mechanisms of homosynaptic long-term potentiation (LTP) and long-term depression (LTD) (Bear et al., 1987; Singer, 1995; Bear, 1998). In the visual cortex and elsewhere, LTP results when presynaptic input activity coincides with a strong postsynaptic response and LTD results when presynaptic input activity coincides with a weak postsynaptic response (reviewed by Bear and Kirkwood, 1996). The level of postsynaptic response at which the sign of the synaptic modification changes from depression to potentiation is called the modification threshold, θ_m. Competition between asynchronously active inputs (e.g. right and left eyes early in

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development) occurs when the value of θ_m is set appropriately (Cooper et al., 1979). In theory, this can be accomplished by allowing the value of θ_m to vary as a function of the average integrated postsynaptic activity (Bienenstock et al., 1982) and there is experimental evidence supporting this assumption in visual cortex (Kirkwood et al., 1996).

The 'sliding threshold' model for synaptic competition does not exclude an important role for neurotrophins. Indeed, there is evidence from the CA1 region of hippocampus and visual cortex that BDNF is involved in the mechanisms of LTP. Although controversial, there are data indicating that exogenous BDNF can directly potentiate synaptic transmission (Kang and Schuman, 1995; Akaneya et al., 1997) and that endogenous BDNF is necessary for the establishment of synaptically induced LTP (Korte et al., 1995; Patterson et al., 1996; Figurov et al., 1996; Akaneya et al., 1997; Kang et al., 1997). BDNF can also modulate synaptic plasticity in the immature hippocampus. Figurov et al. (1996) showed that weak synaptic stimulation, which normally produces no lasting change, induces LTP in the presence of BDNF. These data suggest that exogenously applied BDNF alters the threshold for LTP in the hippocampus.

It was thought that if exogenously applied BDNF affects the value of θ_m in visual cortex, the resulting disruption of synaptic competition could, in principle, account for the disruption of ocular dominance column segregation observed by Cabelli et al. (1995). Therefore, this possibility was examined, using the preparation and approach that were employed previously to demonstrate the effects of visual experience on the value of θ_m (Kirkwood et al., 1996). Specifically, the effects of tetanic stimulation were explored at different frequencies on the sign and magnitude of synaptic change (i.e. LTP/D) in slices of the visual cortex maintained in the presence or absence of exogenously applied BDNF. The data support the idea that one effect of BDNF is to alter the modification threshold for synaptic plasticity. These results were first presented at the 1996 Society for Neuroscience meeting in Washington DC.

1. Methods

1.1. Slice preparation

Long Evans rats (21–28 days old) were anesthetized with the inhalation anesthetic methoxyflurane and decapitated soon after the disappearance of a tail withdrawal reflex. The brain was removed and a block of visual cortex was dissected and sliced in the coronal plane in ice-cold dissection buffer containing (in mM) sucrose, 212; KCl, 2.6; NaH_2PO_4, 1.25; $NaHCO_3$, 26; $MgCl_2$, 5; $CaCl_2$, 0.5; dextrose, 10; kynurenic acid; 10. Slices (400 μm-thick) were allowed to recover in a holding chamber for 1–2 h at room temperature in artificial cerebrospinal fluid (ACSF) containing (in mM) NaCl, 124; KCl, 5; NaH_2PO_4, 1.25; $NaHCO_3$, 26; $MgCl_2$, 1; $CaCl_2$, 2; dextrose, 10. The ACSF and dissection buffer were saturated in 95% O_2, 5% CO_2.

1.2. BDNF treatment

Human recombinant BDNF was a generous gift from Regeneron. BDNF was obtained as a 1 mg/ml solution, in phosphate buffered saline. This solution was aliquoted and stored at −80°C. Aliquots of BDNF were thawed and diluted first to 0.1 mg/ml in ACSF containing 1% bovine serum albumin (BSA) and then to 100–200 ng/ml in a slice incubation chamber containing ACSF and 1% BSA. BDNF (0.1 mg/ml in BSA-containing ACSF) was stored at 4°C for no more than 3 days. In most experiments, slices were transferred from the holding chamber to an incubation chamber containing ACSF with either BSA (1%) or BSA plus BDNF (diluted to 100–200 ng/ml) for 2–5 h prior to electrophysiological analysis. BSA was used as a carrier protein to prevent the loss of BDNF due to nonspecific binding to the incubation chamber. For analysis of LTP and LTD, slices were then transferred to an interface recording chamber, maintained at 30°C and perfused with ACSF at a rate of 1–2 ml/min. For experiments in which the acute effects of BDNF on synaptic physiology were examined, slices were placed in an interface or submerged recording chamber, maintained at 30°C and perfused with ACSF at a rate of 2–4 ml/min. In experiments using the submersion chamber, BDNF was washed on without BSA, due to inadequate drainage of the BSA-containing ACSF. However, teflon tubing was used in all experiments to reduce loss of BDNF.

1.3. Electrophysiology

Extracellular electrodes (filled with ACSF; 1.0 MΩ) placed in layer II/III monitored field potentials (FPs) evoked with a stimulating electrode (concentric bipolar tungsten) placed in the center of the cortical thickness previously histologically confirmed to correspond with layer IV and upper layer V (Aizenman et al., 1996). Changes in the amplitude of the maximum negative field potential were used to measure the magnitude of LTP and LTD. The FPs were digitized at 20 kHz, stored and analyzed using Experimenter's Workbench (DataWave Systems, Boulder, CO). Stable baseline responses were elicited 4/min at a stimulation intensity yielding 50–60% of the maximal response. The stimulation intensities ranged from 10–50 μA. The theta burst stimulation (TBS) consisted of ten bursts at 5 Hz, each burst containing four pulses at 100 Hz,

given four times at 10 s intervals. The 20 Hz tetanus consisted of 40 pulses at 20 Hz given three times at 10 s intervals. LTD or depotentiation was induced with 900 pulses at 1 Hz.

1.4. Data analysis

Only experiments which had a stable baseline amplitude ($< 5\%$ change in 20 min) were included in the analysis. Individual experiments were normalized to a 10 min pre-conditioning baseline period and averaged across experiments. For each slice, a value of potentiation/depression was calculated by averaging the normalized baseline amplitude values 25–30 min after conditioning stimulation. Independent t-tests were used to determine significant differences between BDNF and control groups. The averaged data ($\pm$ S.E.M.) is plotted in all figures. Cumulative histograms were constructed by calculating the percentage change 25–30 min after tetanus and ranking these values in order to show the fraction of cases demonstrating potentiation. A three factor analysis of variance was performed to determine significance of BDNF effects on FP amplitudes during 20 Hz stimulus trains. The three factors were BDNF treatment, pulse number and train number.

2. Results

Previous work in the hippocampus showed that prolonged incubations in BDNF produced a facilitation of LTP (Figurov et al., 1996). Therefore, to test the effects of BDNF on the magnitude of LTP in visual cortex, slices were incubated in ACSF containing BDNF (100–200 ng/ml, 1% BSA) or ACSF with BSA only, for 2–5 h. The BSA was used as a carrier protein to prevent the loss of BDNF due to non-specific binding of BDNF to the tubing, slice chamber, etc. The BSA alone did not affect synaptic transmission, LTP or LTD magnitude. Following the incubation period, slices were transferred to the recording chamber and FP recordings were obtained in layer II/III in response to stimulation of layer IV. To determine if BDNF facilitates the induction of LTP in the visual cortex, a 'weak' 20 Hz tetanus was first utilized (40 pulses, repeated three times at 10 s intervals) which induces significant but not maximal, potentiation (Kirkwood et al., 1996). In control slices, 20 Hz induced small potentiation 30 min after the tetanus ($106 \pm 3\%$ of baseline FP amplitudes; $n = 11$; Fig. 1A). The average LTP magnitude was doubled in slices treated with 100 ng/ml BDNF ($112 \pm 2\%$; $n = 14$; $P < 0.05$). To determine if further enhancement could be observed with higher concentrations of BDNF, these experiments were repeated using 200 ng/ml BDNF. An enhancement of LTP induced with a 20 Hz tetanus was observed ($115 \pm 2\%$; $n = 19$; $P < 0.05$; Fig. 1B) as compared to same day control slices ($107 \pm 2\%$; $n = 16$) but this enhancement was not greater than that observed with 100 ng/ml ($P > 0.05$). The effect of BDNF on LTP elicited with a 'strong' tetanus, theta burst stimulation (TBS), was next examined. TBS typically induces a maximal (saturated) amount of LTP (Kirkwood and Bear, 1994). In contrast to the enhancement observed with the 20 Hz tetanus, incubation of slices in BDNF (200 ng/ml) did not enhance the magnitude of LTP induced with TBS ($119 \pm 4\%$; $n = 6$; Fig. 1C) as compared to control slices ($123 \pm 4\%$; $n = 6$; $P > 0.5$; Fig. 1C). Taken together, these data suggest that BDNF increases the probability of potentiation in response to a suboptimal tetanus but not the maximum attainable level of LTP.

Work in the hippocampus indicates that BDNF treatment facilitates LTP induction by enhancing synaptic responses during high frequency stimulus trains (Figurov et al., 1996). Therefore the FPs during the 20 Hz tetanus were analyzed to determine if the enhancement of LTP by BDNF in the visual cortex could also be attributed to modulation of the synaptic responses during repetitive stimulation. The FP amplitudes were analyzed at different times during each of the 20 Hz trains. The responses to the 2nd, 10th and 40th pulse during the trains were normalized to the baseline FP amplitude for each slice. As shown in Fig. 2, FP amplitudes are typically suppressed during the 40 pulse train. A comparison of BDNF-treated and control slices using a three-factor (treatment, train number and pulse number) ANOVA revealed that suppression of the responses during the trains was significantly less in the BDNF group ($F(1,99) = 10.33$, $P < 0.002$). This difference is most obvious for the tenth response in each train, although the interaction of pulse number and treatment did not reach statistical significance ($P < 0.09$). These results suggest that BDNF enhances LTP induction by enhancing synaptic responses (depolarization) during high frequency stimulation.

High-frequency stimulation induces LTP because it results in a large postsynaptic depolarization, strong activation of NMDA receptors and a large postsynaptic Ca^{2+} influx. However, as stimulation frequency and the resulting level of postsynaptic depolarization is reduced, LTD rather than LTP is induced (Dudek and Bear, 1992). This form of LTD is a specific consequence of attaining during tetanic stimulation a level of NMDA receptor activation and Ca^{2+} influx that is greater than zero but below the threshold for producing LTP (Cummings et al., 1996). Since BDNF treatment alters the responses to repetitive stimulation, it was of interest to know what effect the neurotrophin would have on LTD induced with low-frequency tetanic stimulation (LFS) in the visual cortex.

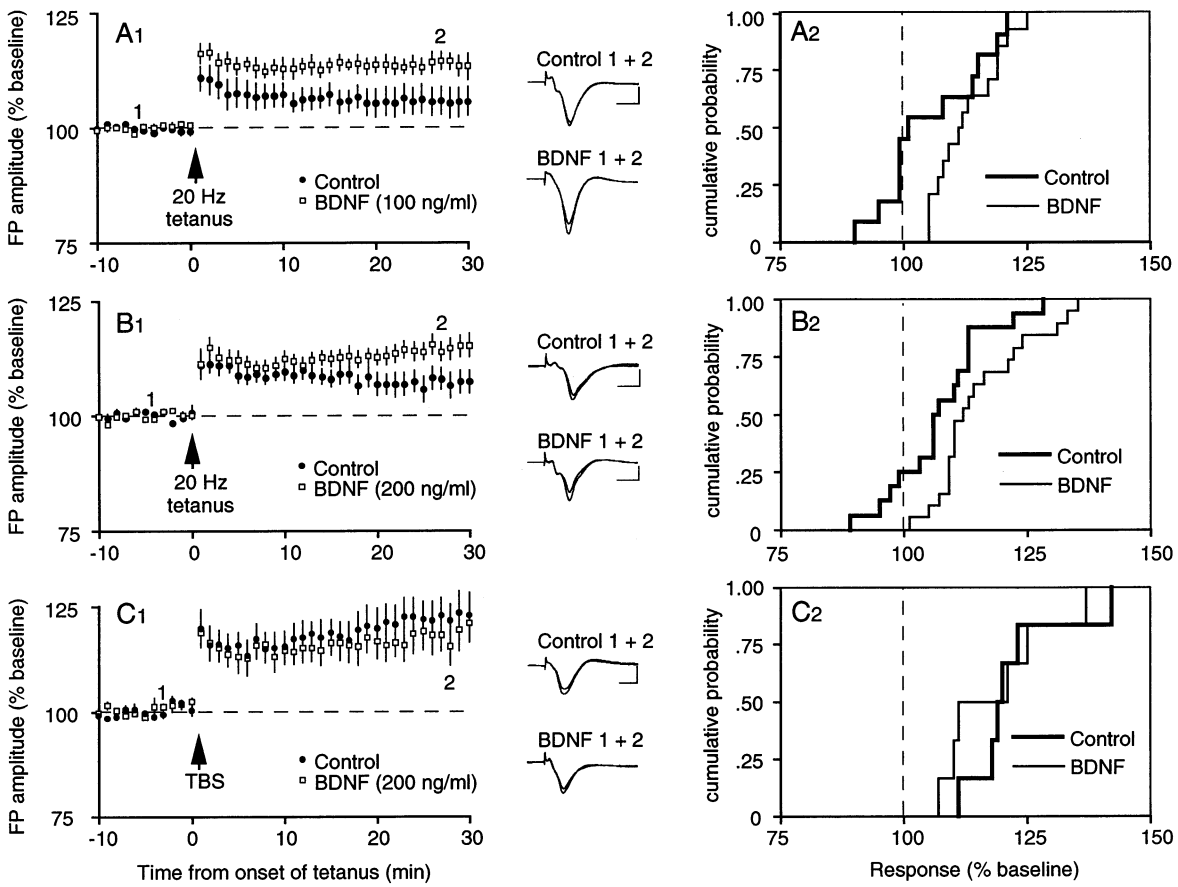

Fig. 1. BDNF facilitates induction of long-term potentiation with a 20 Hz tetanus. A. Slices were incubated for 2–5 h in ACSF containing 100 ng/ml BDNF and 1% BSA or 1% BSA alone. Then recordings were made of layer II/III FPs in response to stimulation of layer IV. A1: A 20 Hz tetanus produced, on average, significantly greater potentiation of synaptic FPs in slices treated with BDNF. Representative FPs (average of five consecutive sweeps) taken at the times indicated before and after the tetanus are superimposed. Scale bars: 0.5 mV, 5 ms. A2: Cumulative probability distribution of the normalized FP amplitudes 30 min after the tetanus for each slice studied in both groups. B. The effects of a 20 Hz tetanus in slices incubated in 200 ng/ml BDNF. All conventions are as for A1. C. The effects of TBS in slices incubated in 200 ng/ml BDNF. All conventions are as for A1.

In the visual cortex, LFS (900 pulses at 1 Hz) causes the same amount of synaptic depression regardless of whether or not LTP has been induced previously (Kirkwood et al., 1996). Therefore, to conserve animals and BDNF, the effects of LFS were investigated in the same slices used for studying the effects of 20 Hz stimulation. At least 30 min elapsed between the 20 Hz tetanus and the onset of 1 Hz stimulation. The results are summarized in Fig. 3. Incubation in BDNF (200 ng/ml; 2–5 h) greatly reduced the magnitude of LTD ($99 \pm 4\%$ of pre-LFS baseline; $n = 11$; $P < 0.05$) as compared to control slices ($87 \pm 1\%$; $n = 7$). As observed with 20 Hz stimulation, synaptic responses were less depressed during LFS in BDNF-treated slices (average amplitude of the final 60 pulses: $65 \pm 2\%$ of pre-LFS baseline; $n = 11$; $P < 0.05$) as compared to control slices ($55 \pm 2\%$; $n = 7$). These results show that BDNF can modulate both activity-dependent increases and decreases in synaptic strength. The effects of BDNF may be attributed to an enhancement of synaptic responses during conditioning stimulation which, in effect, alters the function relating presynaptic stimulation frequency and long-term changes in synaptic strength (Fig. 4).

Several groups have reported acute and long-lasting effects of BDNF on synaptic transmission, both in brain slices and cultured neurons (Lohof et al., 1993; LeBann et al., 1994; Kang and Schuman, 1995; Levine et al., 1995; Akaneya et al., 1997; Carmignoto et al., 1997). Therefore, it was of interest to know if acutely applied BDNF induces potentiation of synaptic responses in the visual cortex. After a stable baseline period, BDNF (200 ng/ml in 1%; BSA) was applied to visual cortical slices for 30 min and responses were monitored for a further 30 min after the cessation of BDNF application. In no case was there any acute or lasting effect of BDNF on response amplitude (Fig. 5A; $n = 6$). The BDNF-induced enhancement of synaptic transmission is reported to be dependent on the flow rate and type of slice chamber used (Kang and Schuman, 1995). Therefore, the effects of BDNF on synaptic transmission were also tested using high (4 ml/min) flow rates and submerged slices. However, in no case was

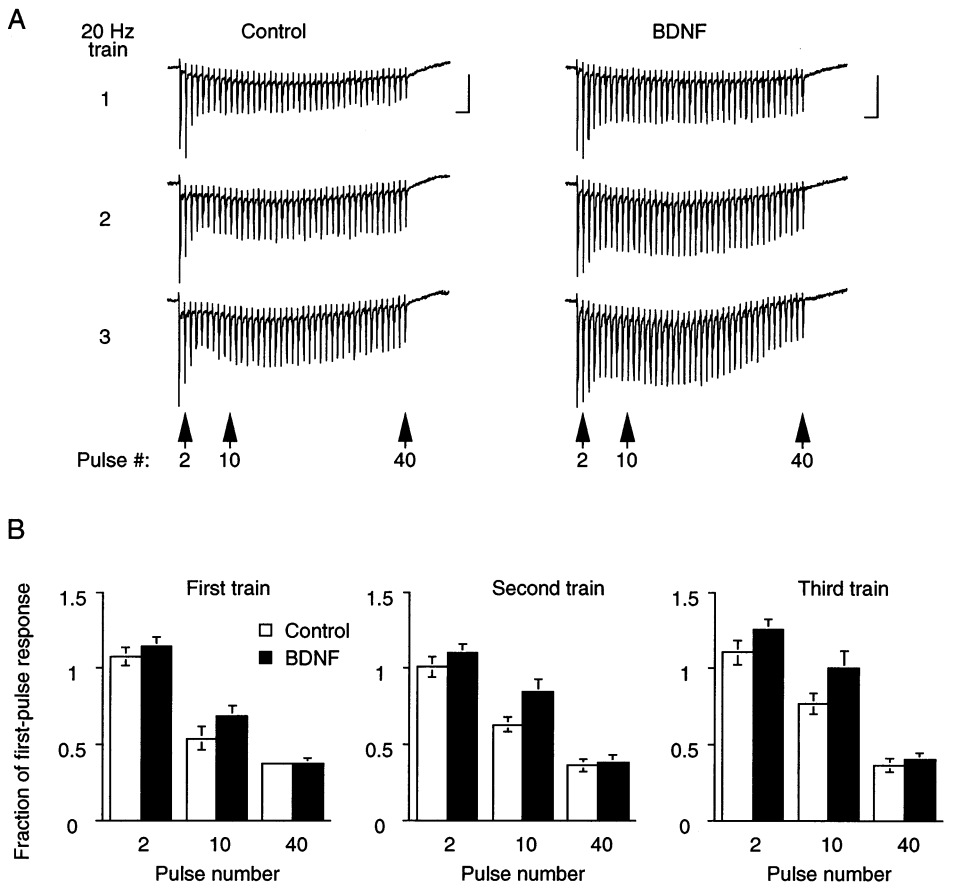

Fig. 2. BDNF reduces the fatigue of synaptic transmission during a 20 Hz tetanus. A. Representative FP responses to the three trains of 20 Hz stimulation used to induce LTP. Scale bars: 0.5 mV, 0.1 s. B. To compare responses during the trains across experiments, the FPs were normalized to the baseline amplitude and averages were calculated of the responses to the 2nd, the 10th and the 40th pulse during each train. There was significantly less depression of synaptic transmission during the trains in BDNF-treated slices ($n = 14$) than in controls ($n = 11$). Performing an ANOVA on these data found a significant effect of BDNF on FP amplitudes ($F(1,99) = 10.33$, $P < 0.002$) but there was no significant interaction of BDNF and pulse number ($P > 0.05$).

any enhancement of synaptic transmission observed (Fig. 5B; $n = 3$).

3. Discussion

The major findings of this study may be summarized as follows. First, treating the visual cortical slices with BDNF for 2–5 h reduces the fatigue of synaptic transmission during prolonged tetanic stimulation at 1 and 20 Hz. Second, BDNF-treated slices show enhanced probability of LTP in response to a 20 Hz tetanus but no difference in the maximal level of the LTP achieved with brief 100 Hz bursts of stimulation (TBS). Third, BDNF-treated slices show less LTD in response to 1 Hz stimulation. Fourth, acutely applied BDNF under the conditions of these experiments fails to cause synaptic potentiation in the visual cortex. Taken together, these data show that several hours of BDNF exposure is sufficient to alter the properties of synaptic plasticity in the visual cortex such that LTP is facilitated and LTD is inhibited over a range of stimulation frequencies (Fig. 4).

3.1. Modulation of LTP and LTD by BDNF

These results show that BDNF lowers the threshold for induction of LTP without affecting the maximal level of potentiation. Similar findings have been obtained in the hippocampus, where BDNF treatment enhances LTP induced with four bursts of TBS but not ten (Figurov et al., 1996). This facilitation of LTP in response to tetanic stimulation could be explained by the BDNF enhancement of synaptic responses during tetanic stimulation, which presumably lead to greater postsynaptic depolarization and Ca^{2+} influx. This modulation of synaptic transmission could occur via a presynaptic mechanism, e.g. by increasing the size of the reserve pool of synaptic vesicles or via a postsynaptic mechanism, e.g. by the enhancement of NMDA receptor-mediated currents (Jarvis et al., 1997; Suen et al., 1997). Alternatively, BDNF may activate downstream second

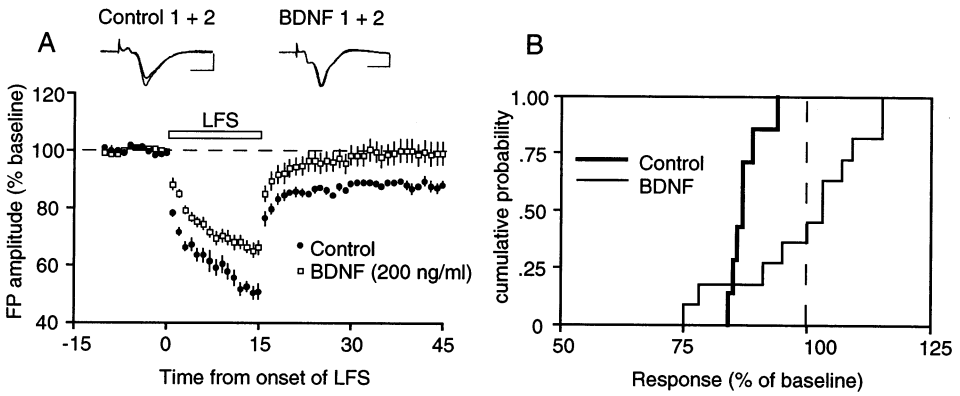

Fig. 3. BDNF reduces LTD in response to 1 Hz stimulation. A. Slices incubated for 2–5 h in ACSF containing 200 ng/ml BDNF and 1% BSA showed significantly less synaptic depression during and after LFS than slices incubated in BSA alone. Representative FPs (average of five consecutive sweeps) taken at the times indicated before and after the LFS are superimposed. Scale bars: 0.5 mV, 5 ms. B. Cumulative probability distribution of the normalized FP amplitudes 30 min after the LFS for each slice studied in both groups.

messenger pathways which contribute to the expression of LTP (Finkbeiner et al., 1997; Kang et al., 1997).

While this study was in progress, two papers were published by Akaneya and colleagues (Akaneya et al., 1996, 1997) on the effects of BDNF in slices of the visual cortex. In contrast to what was observed in the present study, these workers found that BDNF facilitated LTP induced with TBS. However, in their experiments TBS induced only a small magnitude of LTP ($107 \pm 2\%$), similar to what was observed with a 20 Hz tetanus. Thus, under the conditions used by Akaneya et al., the TBS may not be inducing a saturating amount of LTP so an enhancement with BDNF can be observed.

These experiments confirm that BDNF incubation can also reduce the magnitude of LTD induced with 1 Hz stimulation (Akaneya et al., 1996). The reduction of LTD, taken together with the frequency-dependent modulation of LTP, indicate that BDNF shifts the frequency dependence for synaptic strength changes to the left, promoting LTP and reducing LTD. It is unknown if BDNF abolishes LTD or if it changes the optimal frequency of conditioning stimulation required for LTD induction. More experiments testing lower frequencies of conditioning stimulation in the presence of BDNF are needed to differentiate between these possibilities.

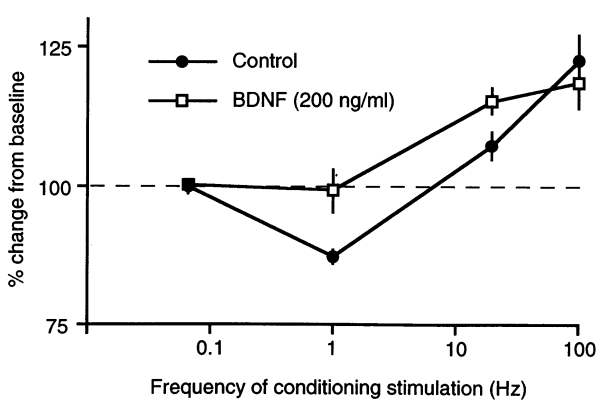

Fig. 4. BDNF treatment shifts the function relating stimulation frequency and synaptic plasticity in the visual cortex. Each data point is the average ($\pm$ S.E.M.) change from baseline 30 min after a tetanus at the indicated frequency.

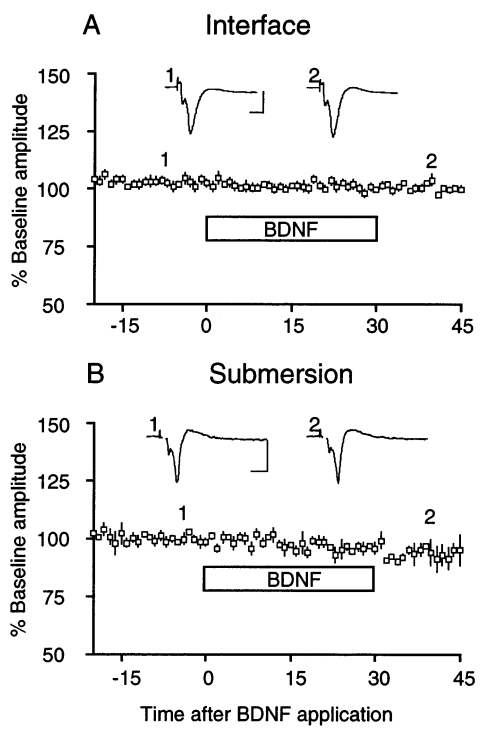

Fig. 5. Acutely applied BDNF fails to alter synaptic transmission. A. Slices maintained in an interface chamber and superfused with 200 ng/ml BDNF in 1% BSA at a rate of 2 ml/min ($n = 6$). Representative FPs (average of five consecutive sweeps) taken at the times indicated before and after the BDNF are displayed. Scale bars: 1 mV, 5 ms. B. Slices maintained in a submersion chamber and perfused with BDNF at a rate of 4 ml/min. Average includes 2 slices perfused with 200 ng/ml and one slice perfused with 20 ng/ml. In no case was a potentiation observed. Representative FPs (average of five consecutive sweeps) taken at the times indicated before and after 200 ng/ml BDNF displayed. Scale bars: 0.5 mV, 5 ms.

3.2. Absence of direct synaptic potentiation in response to BDNF in visual cortex

Some groups have reported a direct potentiation of synaptic transmission by BDNF in both hippocampus and visual cortex (Kang and Schuman, 1995; Akaneya et al., 1997), while others have failed to make similar observations (Figurov et al., 1996; Tanaka et al., 1997). In the present experiments, no effect of acute application of BDNF was observed for 30 min. Although a submersion slice chamber with a high (4 ml/min) flow rate was used to optimize BDNF penetration into the slices, it is possible that the failure to observe potentiation may be due to failure of BDNF to penetrate the slices (Patterson et al., 1996).

It was established that BDNF penetrated into slices that were incubated for 2–5 h, since clear consequences of BDNF treatment were observed. However, even in these experiments no indication that BDNF had potentiated synaptic transmission was seen. First, the level of LTP following TBS was no different in BDNF-treated and control slices, suggesting that BDNF had not caused any change that exhausted the saturable LTP mechanism. Second, there were no significant differences in the stimulation currents required to evoke half-maximal FPs or in the FP amplitudes at half-maximal stimulation intensity, in BDNF-treated slices as compared with controls. Therefore, it is concluded that under the conditions of the experiments, BDNF does not directly potentiate synaptic transmission in the visual cortex.

3.3. The functional significance of BDNF modulation of synaptic plasticity in visual cortex

Although the responses of layer II/III neurons in rat visual cortex were examined, LTP and LTD with identical properties also occur in layer IV neurons (Crair and Malenka, 1995) and in cat visual cortex (Kirkwood et al., 1993; Dudek and Friedlander, 1996). If these findings with BDNF generalize to synaptic plasticity in cat layer IV, they could offer a potential explanation for the finding that infusion of excess BDNF prevents the normal segregation of thalamic axons into ocular dominance columns (Cabelli et al., 1995). Specifically, by facilitating synapse strengthening, BDNF treatment could lead to stabilization of inputs with a low activity level—inputs which would normally weaken and retract. In considering this hypothesis it is important to note that the BDNF TrkB receptor is highly expressed by neurons in layer II/III but is low in layer IV neurons (Cabelli et al., 1996; Cellerino et al., 1996; Yan et al., 1997). However, the lateral geniculate nucleus (LGN) neurons that provide the afferent innervation of layer IV do contain TrkB during the period of ocular dominance column formation (Cabelli et al., 1996). Thus, BDNF enhancement of presynaptic processes in LGN afferents could, as described in the current study, alter the relationship of input activity and synaptic plasticity. Of course, the equally interesting alternative is that BDNF modulation of plasticity is confined to the superficial layers where it is relevant to refinement of intracortical circuits, such as those that contribute to orientation selectivity (Galuske et al., 1996).

Modulation of the synaptic modification threshold could be a mechanism by which endogenous BDNF contributes to the activity-dependent development of the visual cortex. BDNF is synthesized and released in an activity-dependent manner (Isackson et al., 1991; Zafra et al., 1991; Castren et al., 1992; Bozzi et al., 1995; Schoups et al., 1995; Androutsellis et al., 1996; Heymach et al., 1996) and, the present results suggest that it promotes the strengthening of active synapses. Thus, the activity and BDNF may act in concert to strengthen and stabilize synapses. A synergistic effect of activity and BDNF has been observed in other preparations. In the visual cortex slice cultures, activity is required to observe BDNF enhancement of dendritic growth (McAllister et al., 1996) and activity also enhances the survival-promoting effects of BDNF in dissociated cortical neurons (Ghosh et al., 1994). However, in order to understand if the activity-dependent release of endogenous BDNF normally contributes to regulation of synaptic plasticity in the visual cortex, it will be important in future LTP/D experiments to test the effect of the TrkB-IgG fusion protein, which binds and inactivates endogenously released BDNF (Shelton et al., 1995; Akaneya et al., 1997).

The data are clear that BDNF can be regarded as a 'pleiotrophin', with diverse actions on the developing visual cortex. In addition to its effects on cell survival, dendritic growth and synaptic plasticity, BDNF is also implicated in the activity-dependent development of GABAergic neurons in the cortex (Marty et al., 1997; Rutherford et al., 1997). In developing an overall view of the role of neurotrophins in the visual cortical development, it will be important to understand how the acute and chronic actions of BDNF fit together. Future studies, aimed at providing a link between the acute effects of BDNF on synaptic transmission and the long-term effects on growth and survival of neurons, should greatly increase the understanding of the complex role of neurotrophins in development.

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