To BDNF or Not to BDNF: That Is the Epileptic Hippocampus

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Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, has drawn much attention as a potential therapeutic target for temporal lobe epilepsy (TLE). TLE seizures are produced by synchronized hyperactivity of neuron populations due to the disruption of a balance between excitatory and inhibitory synaptic transmissions. In epileptogenesis-related brain areas, including the hippocampus, BDNF is up-regulated in the course of the development of epilepsy and induces a collapse of balanced excitation and inhibition, eventually exerting its epileptogenic effects. On the other hand, several reports demonstrate that intrahippocampal infusion of BDNF can attenuate (or retard) the development of epilepsy. This antiepileptogenic effect seems to be mediated mainly by an increase in the expression of neuropeptide Y. These contrasting effects of BDNF have prevented us from concluding whether inhibition or enhancement of BDNF signaling finally achieves the prevention of TLE. To address this question, it is essential to evaluate how BDNF changes its influences depending on conditions, for example, cell specificity, neural networks, and expression timing and loci. In this article, the authors review BDNF-induced acute and long-lasting changes seen in epileptic circuits from the anatomical and functional points of view. NEUROSCIENTIST 11(4):282–287, 2005. DOI: 10.1177/1073858405278266

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Epilepsy is a neurological disorder characterized by chronic recurrent seizures and based on anatomical and physiological aberrations of a set of neurons that generate highly synchronized activity. Temporal lobe epilepsy (TLE) is the most prevalent type of refractory epilepsy and is characterized by complex partial seizures. The limbic system, including the hippocampus, is thought to play a pivotal role in the initiation and propagation of TLE seizures (Fig. 1; Wieser and others 1993). Patients with TLE often exhibit antiepileptic drug resistance and hence are subjected to surgical operations.

Several studies have focused on the understanding of the cellular and molecular mechanisms underlying this disorder to eventually develop better therapeutic treatments. One of the most studied molecules in this field is the neurotrophin brain-derived neurotrophic factor (BDNF). Expression of BDNF mRNA (Murray and others 2000) and protein (Takahashi and others 1999) has been reputed to be elevated in the hippocampal and temporal lobe tissues from human epileptic brains. Western blot analysis with proteins present in the postsynaptic density from the human epileptic neocortex revealed that TrkB, the high-affinity receptor for BDNF, is also up-regulated to 2.6 ± 0.26-fold (SEM) compared with control patients (Wyneken and others 2003). Similar results have generally been replicated in several types of animal TLE models. However, whether such up-regulation of BDNF facilitates or prevents TLE remains to be clarified. In addition to the well-known physiological actions of BDNF, reevaluation of how BDNF acts in epileptic brains may help in the design of more effective therapies for epilepsy.

BDNF Enhances Excitatory Neurotransmission

One of the well-established effects of BDNF on the hippocampus is a rapid modulation of excitatory and inhibitory synaptic transmission. In cultured hippocampal neurons, BDNF increases spontaneous firing rates more than twofold, leading to an increase in both the amplitude and frequency of excitatory postsynaptic currents (EPSCs) within two to three minutes of application (Levine and others 1995). BDNF also enhances excitatory transmission in adult hippocampal slices; it increases field excitatory postsynaptic potentials (EPSPs) at Schaffer collateral-CA1 pyramidal cell synapses (Kang and Schuman 1995). Results from our laboratory showed that BDNF increases neural excitability of CA1 pyramidal cells by inhibiting $GABA_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs); both evoked and spontaneous IPSC sizes were attenuated a few minutes after BDNF application (Tanaka and others

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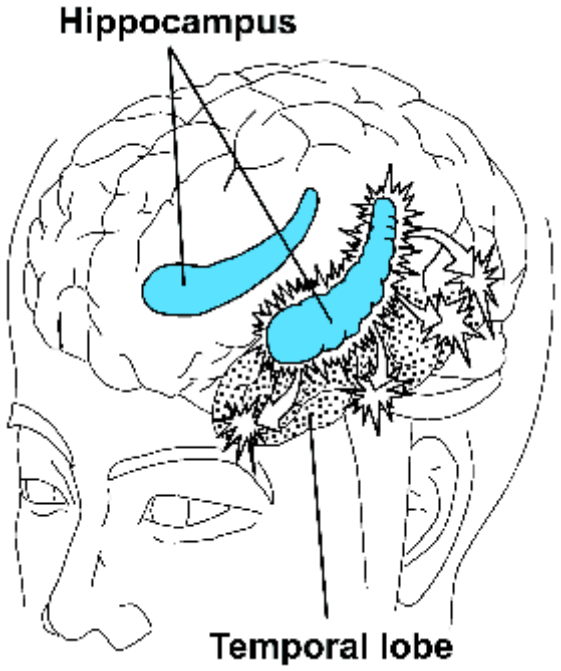

Fig. 1. Human brain with temporal lobe epilepsy (TLE). In the brain of a TLE patient, abnormally synchronized activity of the neuron population occurs in the hippocampus and propagates over the temporal lobe of the cerebral cortex, resulting in systemic seizures.

1997). These effects of BDNF are all blocked by the tyrosine kinase inhibitor K252a and thus are mediated by TrkB receptor activity.

Investigating the role of BDNF in hippocampal CA3 is especially important because the mossy fiber (MF) axon of dentate granule cells, which innervates dendrites of CA3 pyramidal cells, contains high levels of BDNF under basal conditions, and this level of BDNF undergoes further up-regulation after seizure onsets, induced by an injection of the convulsant kainic acid (Rudge and others 1998). One hour after the bath application of BDNF to entorhino-hippocampal slices, population spikes evoked in the CA3 area by granule cell layer stimulation show a greater than twofold increase in amplitude (Scharfman 1997). Furthermore, after a two-hour application of BDNF, paired-pulse stimulation of the granule cell layer causes multiple population spikes in CA3, which are never observed in the absence of BDNF. This implies that BDNF, when up-regulated in epileptic brains, may induce an abnormal enhancement of excitability of CA3 pyramidal cells (Scharfman 1997).

Proepileptogenic Effects of BDNF in the Epileptic Brain

It is extremely important to know how BDNF works in the epileptic hippocampus. In TLE, hippocampal circuits undergo anatomical and physiological reorganization, and it is not hard to imagine that these alterations change the mode of the BDNF action. Among reorganizations seen in the epileptic hippocampus, such as hippocampal sclerosis, neuronal cell loss, gliosis, and perhaps neurogenesis, MF sprouting is consistent and highly remarkable. The MF axons normally arise from the dentate granule cells and make synapses with hilar and CA3 neurons, but under epileptic conditions, they often branch out of the dentate hilus, are projected abnormally to the inner molecular layer, and provide synaptic contacts therein with the dendrites of granule cells, a phenomenon that is termed the MF sprouting (Fig. 2). The majority of these abnormal synapses are excitatory, and as a result, hyperexcitable recurrent loops are formed in the dentate gyrus (Koyama and Ikegaya 2004).

The dentate gyrus is believed to serve as a high-resistance gate and block invasion of epileptiform activity from the entorhinal cortex to the hippocampus. This "fail safe–like" property is rendered by the static characteristics of dentate granule cells; that is, they have hyperpolarized resting membrane potential, high K^+ conductance, low Ca^{2+} conductance, strong tonic and phasic GABA inhibition, and lack of the intrinsic capacity for burst discharges (Nadler 2003). The malfunction of this gate would bring about overexcitation of the hippocampus (Koyama and Ikegaya 2004).

Scharfman and colleagues (1999) used hippocampal slice preparations obtained from pilocarpine-induced epileptic rats, which showed MF sprouting and BDNF up-regulation, to investigate the effect of BDNF on the epileptic dentate gyrus. They found that BDNF enhances the excitability of granule cells through the activation of TrkB; a 30- to 60-minute application of BDNF induces multiple population spikes in the granule cell layer in response to a stimulus of the dentate hilus, and it also induces spontaneous population spikes. BDNF–elicited hyperexcitability is also confirmed by whole-cell patch-clamp recordings from dentate granule cells in slices prepared from human TLE patients (Zhu and Roper 2001). In the presence of the $GABA_A$ receptor blocker picrotoxin, BDNF increases the frequency and amplitude of spontaneous EPSCs as early as 30 seconds after the start of BDNF application, and this effect reaches its maximum after a few minutes and lasts for at least one hour even after removal of BDNF. BDNF also increases the size of EPSCs evoked by perforant pathway stimulation. However, this has not yet been tested in human normal hippocampal tissues, and it remains unclear whether the BDNF enhancement of cortical inputs is a specific effect in human TLE tissues. Zhu and Roper (2001) further observed that in the presence of the glutamate receptor antagonists CNQX and AP5, BDNF has no effect on spontaneous IPSCs in granule cells, but it readily decreases the amplitude of perforant path-evoked IPSCs. These results are suggestive of the positive contribution of BDNF to epileptogenesis in TLE patients.

Recently, we observed that MF sprouting itself can be induced by BDNF in vitro (Koyama and others 2004). Cultured hippocampal slices display robust MF sprouting and abnormal excitability of dentate granule cells when treated with picrotoxin for 10 days in vitro. In these cultures, BDNF protein was up-regulated specifically in the MF pathway, an effect that is similar to that

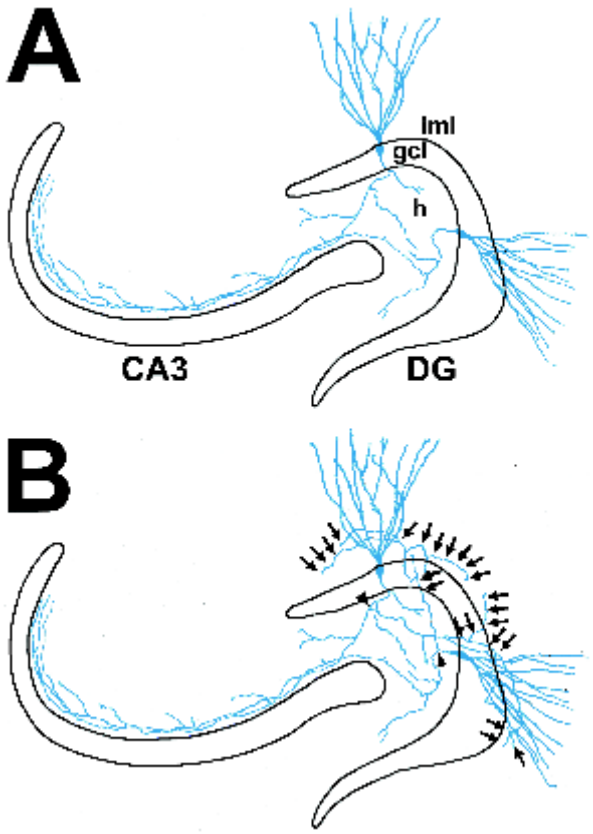

Fig. 2. Sprouting of hippocampal mossy fibers (MFs). *A*, Normal MF projection. Granule cells in the dentate gyrus extend their MF axons through the dentate hilus into the CA3 area and make synapses with hilar neurons and CA3 neurons. *B*, In the hippocampus of a temporal lobe epilepsy (TLE) patient, MFs branch out in the dentate hilus (arrowheads), run across the granule cell layer (gcl), and make synapses with dendrites of granule cells in the inner molecular layer (arrows), a phenomenon that is called "MF sprouting." MF sprouting makes up hyperexcitable reentrant circuits in the dentate gyrus, which are believed to serve as epileptic foci. DG = dentate gyrus; h = hilus; iml = inner molecular layer.

observed in epilepsy patients or model rats. Mossy Fiber sprouting is prevented by the coapplication of K252a or function-blocking anti-BDNF antibody. Importantly, even without neural activity, MF sprouting can occur when a BDNF-including bead is placed on the dentate hilus. We therefore conclude that BDNF induces the branch-out of hilar axonal shafts. This notion is supported by the fact that in primary granule cell cultures, BDNF increases the density of phalloidin-positive protrusions along τ-1-positive MF axons and that this effect is attenuated by overexpression of truncated TrkB receptors that lack the intracellular tyrosine kinase domain and thus serve as a dominant negative form. These results indicate that BDNF plays a causal role in triggering MF sprouting, and they provide morphological evidence for the idea that BDNF contributes to hyperexcitability of the dentate gyrus. Indeed, intrahippocampal infusion of BDNF is reported to induce MF sprouting and seizure activity in the rat (Scharfman and others 2002), although the results are still controversial (Vaidya and others 1999).

BDNF Modulates GABAergic Inhibition in the Epileptic Brain

Although enhancement of excitatory transmission is an outstanding action of BDNF, there is also a report suggesting that BDNF potentiates GABAergic inhibition in human epileptic brain (Palma and others 2005). The authors transplanted $GABA_A$ receptors obtained from TLE patients to the plasma membrane of *Xenopus* oocytes; they injected membrane microvesicles obtained from hippocampal and temporal neocortex tissue homogenates. This procedure preserves the original structure of the receptors and their associated proteins. The microvesicles of an epileptic membrane contain both full-length TrkB and the truncated isoforms. One-hour exposure of BDNF increased the amplitude of the $GABA_A$ receptor–mediated current up to 3.1-fold, as assessed by single GABA applications to oocytes that express TLE patients–derived $GABA_A$ receptors. This effect is not observed in oocytes that express $GABA_A$ receptors of a control patient who does not suffer from epileptic episodes. In $GABA_A$ receptors microtransplanted from TLE patients, repetitive applications of GABA (1 mM; 10-second duration at 40-second intervals) reduce the amplitude of $GABA_A$-mediated currents to 26.2% ± 3.0% (relative to the first GABA application). This rundown of GABA-evoked current is rescued to 79.7% ± 6.0% when the oocytes are preincubated with BDNF for two hours. Pharmacological experiments showed that this recovery is dependent on PLC signaling via the activation of TrkB. This work suggests that BDNF potentiates $GABA_A$ receptor–mediated transmission in epileptic brains. In this experimental system, however, the origin of $GABA_A$ receptors or TrkB is not clear; further investigations are necessary to examine whether BDNF acts in the same fashion in vivo.

It is possible that BDNF reduces the overall activity of hippocampal networks. BDNF is reported to increase the density of inhibitory synapses in hippocampal slice cultures (Marty and others 2000), enlarge the body size of GABAergic neurons, and enhance the expression of glutamic acid decarboxylase (GAD), a GABA-synthesizing enzyme, in cultured hippocampal neurons (Yamada and others 2002). However, chronic intrahippocampal infusion of BDNF did not affect GAD expression in the rat hippocampus in vivo (Reibel, Vivien-Roels, and others 2000), although seizure activity increases GAD expression (Ramirez and Gutierrez 2001). Further investigations are needed to elucidate the link of BDNF to the GABAergic system in the epileptic brain.

Antiepileptogenic Effect of BDNF via Neuropeptide Y in the Epileptic Brain

An antiepileptogenic role of BDNF has been reported by Reibel, Larmet, and others (2000). They reported that

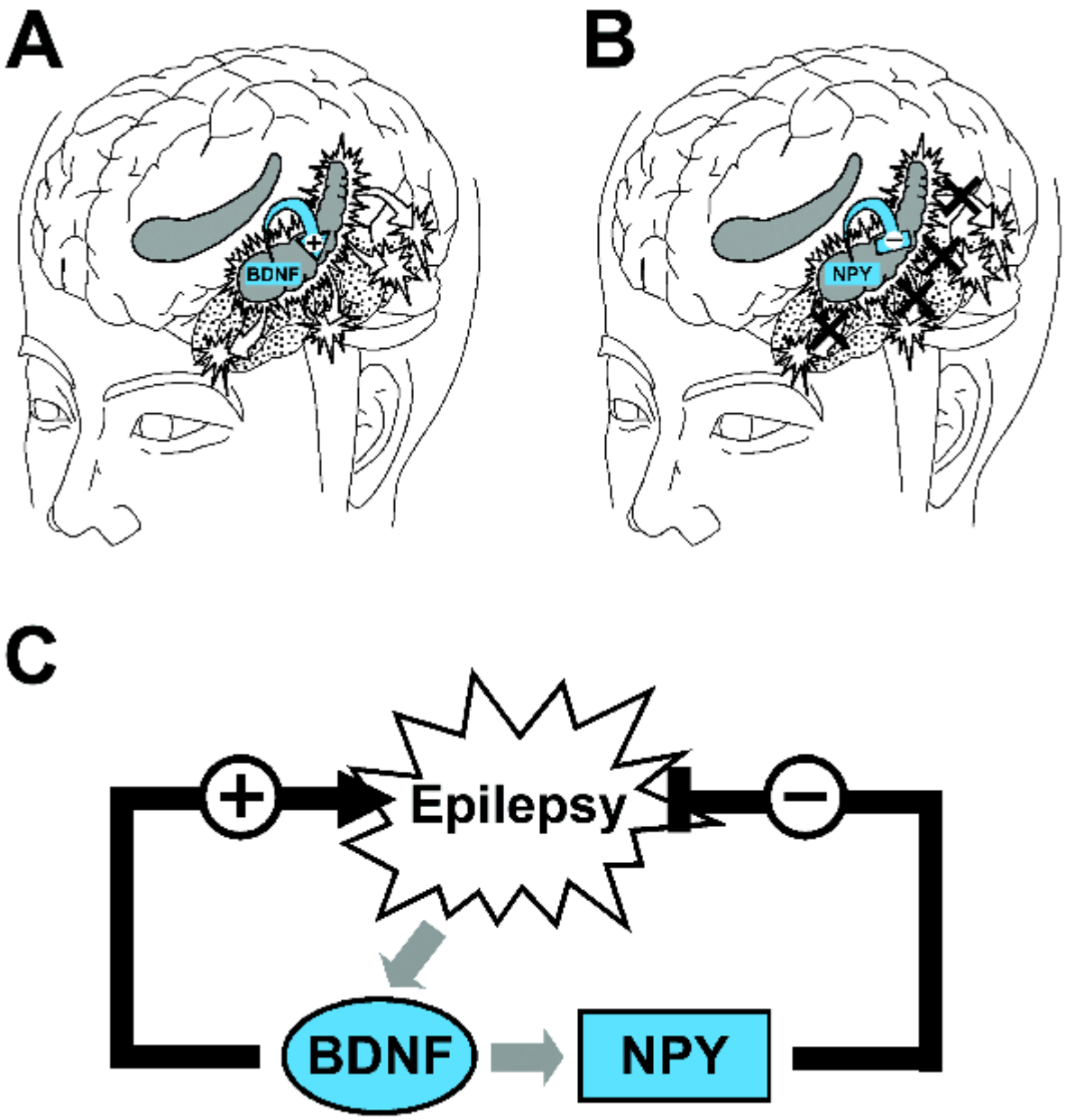

Fig. 3. Brain-derived neurotrophic factor (BDNF) and neuropeptide Y (NPY) play opposite roles in the epileptic hippocampus. *A*, *B*, Schematic diagrams of the roles of BDNF (*A*) and NPY (*B*) in the epileptic brain. BDNF is likely to enhance the excitability of hippocampal networks, whereas NPY suppresses it and thereby blocks seizure propagations into the temporal lobe. *C*, Epileptogenesis involves multiple steps, including the expression of BDNF and NPY. Hyperactivity of neurons in the hippocampus induces the BDNF expression, which in turn up-regulates NPY.

seven-day chronic infusion of BDNF into the adult rat hippocampus significantly delays the development of kindling induced by repeated electrical stimuli, a model of progressive TLE. Although there is the possibility that such prolonged BDNF infusion down-regulates or desensitizes the TrkB signaling pathway, the antiepileptic effect of BDNF is thought to be attributable to neuropeptide Y (NPY). The level of NPY is increased in the neocortex of TLE patients and positively correlated with the BDNF level (Takahashi and others 1999). In rat epilepsy models, BDNF up-regulation in the MF pathway is followed by an increase in NPY in the same brain region (Vezzani and others 1999), suggesting that seizure-induced BDNF triggers NPY expression. Consistent with this idea, intrahippocampal infusion of BDNF for seven days induces NPY up-regulation one week after the end of the infusion (Reibel, Vivien-Roels, and others 2000), and this time course of NPY up-regulation is similar to the effect of BDNF on kindling.

Infusion of NPY into the rat hippocampus retards the development of hippocampal kindling, whereas infusion of anti-NPY immunoglobulins exacerbates it (Reibel and others 2003), and NPY-deficient mice develop spontaneous seizures and show a higher susceptibility to seizures induced by GABA receptor antagonists (Erickson and others 1996). These results are consistent with the idea that epileptogenesis reduced by seizure-induced BDNF in the hippocampus is mediated by the up-regulation of NPY.

In hippocampal slices prepared from rats with pilocarpine-induced status epilepticus, NPY inhibits excitatory recurrent neurotransmission between sprouted MFs and granule cells (Tu and others 2005). Up-regulated immunoreactivity of NPY is present in the MF pathway even 20 weeks after pilocarpine administration. The highest NPY expression is found in the inner molecular layer of the dentate gyrus, in a subregion in which sprouted MFs form synapses with dendrites of granule cells. Interestingly, the inhibitory effect of NPY is synapse type–specific; NPY inhibits sprouted MF-mediated EPSCs via the activation of presynaptic Y_2 receptors, but it does not affect perforant path-mediated or ipsilateral associational commissural-mediated EPSCs in the granule cells. More important, the Y_2 receptor antagonist BIIE0246 alone is capable of increasing the amplitude of sprouted MF-mediated EPSCs and the frequency of miniature EPSCs and of enhancing the degree of MF-evoked epileptiform spiking activity of granule cells. These results indicate that NPY endogenously released from sprouted MF terminals prevents granule cells from firing hypersynchronized discharges and thereby blocks the invasion of seizure activity from the entorhinal cortex to the hippocampus.

Insights From Transgenic Animals

Transgenic animals with altered BDNF-TrkB signaling levels have been helpful in the investigation of the contribution of BDNF to epilepsy in vivo. Kindling development does not occur in *Synapsin-Cre* conditional $TrkB^{-/-}$ mutant mice. On the other hand, epilepsy progress is only partially blocked in conditional BDNF knockout mice. This is probably because other neurotrophins, including NT-3, compensate the level of TrkB activation (He and others 2004). Some, but not all, of transgenic mice overexpressing BDNF by the β-actin promoter display spontaneous motor seizures, which reach stage 5 out of all 8 stages, defined by the severity of seizures; stage 5 animals suffer from severe seizures with prolonged loss of postural control or prolonged tonus (Croll and others 1999). These transgenic mice show more susceptibility to kainic acid, compared with wild-type littermates (7.11 ± 0.35 in tg, 5.00 ± 0.66 in wt mice; $P < 0.05$). Electrophysiological studies reveal that slices from these BDNF-overexpressing mice show the hyperexcitability of the CA3 area and the entorhinal cortex.

Consistent with these results, transgenic mice that overexpress full-length TrkB receptors under the control of the Thy1 promoter exhibit more severe seizures during status epilepticus induced by kainic acid (Lahteinen and others 2003). These results indicated that BDNF/TrkB signaling reduces the threshold for epileptic seizures, presumably via enhancing excitatory transmission. A few months after kainate-induced status epilepticus, however, TrkB-overexpressing mice no longer show a significant exacerbation of the development of epilepsy, as compared with wild-type mice. This suggests that the temporal and spatial patterns of TrkB signaling are crucial in epileptogenesis. In support of this idea, in cultured hippocampal slices, BDNF efficiently induces MF sprouting only when applied locally to the dentate hilus, but BDNF applied to other areas such as the molecular layer and the CA3 area is ineffective, nor does the bath application of BDNF induce MF sprouting (Koyama and others 2004), which indicates that localized activation of BDNF-TrkB signaling is critical for triggering MF sprouting.

Conclusion

Taken together, inhibiting BDNF-TrkB signaling and reinforcing the NPY system in the adult hippocampus seem to be potential therapeutic strategies for TLE (Fig. 3). However, we have to be extremely careful in interpreting the experimental data, especially data obtained from animal models, which often are a mixture of the transient and long-lasting effects of BDNF. We must not forget the fact that epilepsy is fundamentally a chronic disease. The life span of animals and the speed of progress of epilepsy in animals could be very different from those seen in human patients. In this respect, investigations of the action of BDNF in the infant brain could be of particular help in developing new therapies that can prevent incipient epileptogenesis ahead of time because up-regulation of BDNF mRNA is observed in febrile seizure models (Kim and others 2001), and early childhood convulsions are likely to contribute subsequently to adult hippocampal sclerosis (Grünewald 2002).

We also need to pay attention to the individual differences in sensitivity to BDNF. Intrahippocampal infusion of BDNF causes spontaneous seizures only in 25% (8/32) of rats (Scharfman and others 2002), and only some, but not all, of BDNF-overexpressing mice show spontaneous motor seizures (Croll and others 1999). Single nucleotide polymorphisms found in the BDNF gene in humans may also facilitate such individual differences (Egan and others 2003). It is thus obvious that we need to collect more pieces of evidence linking BDNF and epileptogenesis.

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