Brain-derived Neurotrophic Factor and Epilepsy—A Missing Link?

Helen E. Scharfman, Ph.D.

Helen Hayes Hospital, West Haverstraw, New York and Columbia University, New York

It has been known for some time that brain-derived neurotrophic factor (BDNF) is critical to normal development of the CNS, and more recently, studies also have documented the ability of BDNF to modify adult CNS structure and function. Therefore, it is no surprise that BDNF has been linked to diseases, such as epilepsy, which may involve abnormal cortical development or altered brain structure and function after maturity. This review evaluates the evidence, particularly from recent studies, that BDNF contributes to the development of temporal lobe epilepsy (TLE).

Fundamentals

BDNF is one of a family of compounds, termed neurotrophins, which include nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). All neurotrophins bind to the p75 receptor, but their respective actions at p75, at least in the adult brain, are not as well understood as their actions at trk receptors, which include trkA, trkB, and trkC. NGF binds to trkA selectively, and both BDNF and NT-4/5 bind only to trkB. NT-3 has some ability to bind to trkB but is thought to exert its actions primarily at trkC.

When an agonist binds to trkB, receptor dimerization occurs, followed by autophosphorylation of intracellular tyrosine residues. These residues are targeted by diverse intracellular proteins, which activate G proteins and signaling cascades, such as the mitogen-activated protein kinase (MAPK) pathway, activated phospholipase C-γ (PLC-γ), phosphoinositol-3 kinase (PI3K), and calcium/calmodulin-dependent protein kinase II (CaMKII). Ultimately, transcription factor induction occurs, and a primary example is CREB [cyclic adenosine monophosphate (cAMP) response element–binding protein].

Several initial assumptions about neurotrophin receptors are now recognized as oversimplifications. For example, it was originally thought that p75 acted largely independent of trk, but it now has been shown that p75 can interact with trk and that distinct trk forms (i.e., trkA and trkB) may interact with each other (2). Furthermore, truncated forms of trkB, which have been known to exist for some time, initially were considered functionally irrelevant because they lacked the internal catalytic domain. It is now known that truncated trkB can exert biologic effects (3). Similarly, initially it was thought that only full-length neurotrophins were functional, but it now has been shown that proneurotrophins also are bioactive. Proneurotrophins may be particularly relevant to epilepsy because they appear to act preferentially on p75 once they are released (4) and because p75 is upregulated in apoptotic neurons after seizures (5). However, once outside the cell, proneurotrophins are cleaved by serine proteases and matrix metalloproteases, many of which are upregulated after seizures (e.g., PC1, furin) (6), which would favor a greater role of the cleavage product (i.e., BDNF instead of proBDNF).

Historical Overview

The first study on BDNF of relevance to epilepsy demonstrated that seizures greatly increased BDNF expression in areas of the brain that are involved in limbic seizures (7,8). One of the most sensitive cell types appears to be dentate gyrus granule cells, which appear to transport BDNF primarily to their axons and mossy fibers and to contain one of the highest concentrations of BDNF in the normal adult rat (9). However, hippocampal pyramidal cells also increase expression of BDNF after seizures, and interestingly, most other areas known to be vulnerable in TLE (e.g., amygdala, entorhinal cortex, piriform cortex) increase BDNF expression as well (10,11). BDNF upregulation after seizures has now been shown to be extremely robust, regardless of the method used for seizure induction. It now is clear that trkB also increases after seizures and does so in a temporal and spatial pattern that, for the most part, mimics BDNF (10,12). BDNF expression increases after injury or ischemia (13), and this is also the case for trkB, but not other trk receptors (14). In addition, BDNF is increased by relatively benign manipulations, such as exercise (15) or estrogen treatment (16,17).

Independently, other studies have provided potential insight into physiological effects of BDNF that might be relevant to excitability. First in cultures of *Xenopus* myocytes (18) and then in CNS slices of adult rodents (19), it was shown that BDNF application potentiates excitatory transmission. In

Epilepsy Currents, Vol. 5, No. 3 (May/June) 2005 pp. 83–88
Blackwell Publishing, Inc.

adult hippocampus, BDNF induces a long-lasting potentiation of each segment of the trisynaptic circuit (20–22). Additional studies have identified both structural and functional actions on GABAergic neurons (23), but the precise subtypes of affected GABAergic neurons are not yet delineated precisely. It is also not clear what role GABAergic neurons play in the potentiation of glutamatergic input to principal neurons, although evidence that BDNF can decrease GABAergic transmission (24,25) and decrease the K^+–Cl^- cotransporter KCC2 (26) makes it likely that GABAergic neurons play some type of role. Another acute action of BDNF is depolarization of neurons by a rapid action at $Na_v1.9$ (27). This effect is intriguing because it may contribute to long-lasting potentiation of glutamatergic inputs, given the evidence that depolarization in conjunction with high-frequency stimulation facilitates the induction of long-term potentiation. Importantly, there is still considerable controversy regarding actions of BDNF, sites of action (i.e., presynaptic versus postsynaptic), and underlying mechanisms. Moreover, many potential effects of BDNF (e.g., on glia) are unresolved.

Regarding the relevance of BDNF to epilepsy, most, if not all, actions could potentially increase excitability and, indeed, infusion of BDNF in vivo can induce seizures (28), whereas scavenging BDNF in vivo appears to reduce the ability to kindle (29). However, some studies of BDNF infusion in vivo do not support these results, because kindling is delayed after chronic BDNF infusion (30,31). An explanation for the disparity has been suggested by recent studies that show that chronic infusion of BDNF can downregulate trkB receptors, although acute administration of BDNF does not (32).

BDNF and Epilepsy: A Hypothesis

The two concurrent lines of research described earlier: (a) the ability of seizures or injury to increase both BDNF and trkB, and (b) the ability of BDNF to increase excitability of principal cells, led to the following hypothesis for epileptogenesis (33). The first part of the hypothesis envisages an event precipitating TLE, such as an insult, injury, period of febrile seizures, or encephalitis. The prediction is that this initial event elevates BDNF in diverse ways in various areas of the brain that influence limbic networks. Important to this argument is that BDNF is increased not only after insults, injury, or seizures in the adult (as previously discussed) but also after febrile seizures (34). Interestingly, polymorphisms in the BDNF gene have been linked to febrile seizures (35). Regarding changes in BDNF levels after encephalitis, little is known; however, maternal infection can elevate BDNF in the fetus (36), and infection can lead to BDNF synthesis in immune cells that penetrate the CNS (37).

The second part of the hypothesis posits that increased BDNF potentiates glutamatergic transmission, increasing neural activity in limbic circuits. The increased activity would lead to a secondary increase in BDNF/trkB levels and initiate further potentiation. Evidence for the latter comes from in vitro studies showing that long-term potentiation can induce BDNF (38). The supposition is that these events ultimately would escalate, by positive feedback, and reach seizure threshold (33).

At the same time, growth-associated actions of BDNF may occur in a complementary fashion to promote epileptogenesis. This aspect of the hypothesis rests on the large body of evidence demonstrating that BDNF facilitates changes in spines and axons and promotes neurogenesis in the adult brain. Indeed, microarray studies have shown that BDNF is elevated during the latent period and may be one of the growth-associated proteins important in epileptogenesis (39). The primary argument against this hypothesis is that it is not yet known whether growth and morphologic plasticity always leads to a net increase excitability: they could also decrease excitability. What is known is that BDNF administration has the following effects: (a) BDNF increases neurogenesis in the dentate gyrus (40) and ectopic neurogenesis (41); (b) BDNF increases basal dendrite formation of granule cells (42,43); (c) BDNF induces morphologic changes in dendritic spines (44,45); and (d) stimulates axonal growth (42,46). Although these BDNF-induced events modify excitability (47–49), a definitive association with epileptogenesis and chronic epilepsy has not been established.

Complicating Factors in Establishing a Relation between BDNF and Epilepsy

In evaluating the validity of the hypothesis described earlier, various issues both support and argue against it. One argument against the hypothesis is the lack of evidence that BDNF upregulation is sufficient to set into motion the cascade of events leading to spontaneous seizures. Endogenous controls appear to limit the ability of BDNF to increase excitability. For example, BDNF induces neuropeptide Y (NPY) expression, which appears to potently depress synaptic transmission at many of the same synapses that BDNF potentiates (50). Indeed, these effects may be one of the reasons why the epileptic brain does not constantly have seizures. Another example of an inherent "brake" is that trkB decreases under some conditions in which BDNF is elevated, although this relation is not a simple issue because an increase in BDNF does not always decrease trkB (32). In addition, trk can be moved to different cellular compartments and, potentially, have new functional roles (51).

Another important consideration in assessing the validity of the hypothesis is that the types of growth-associated changes

related to elevated BDNF are not necessarily consistent with epileptogenesis, if one examines details of studies to date. For example, BDNF administration fosters dendritic spine changes in organotypic cultures of postnatal rats (45) and increases spines in cultures of postnatal rats (44), but, in some models of epilepsy, a dramatic reduction of spines can occur (47,52). Notably, one study of cortical neurons that expressed BDNF showed that this treatment did decrease spines along dendrites (43). Another example of potential discordance relates to the ability of BDNF to increase axonal growth. Evidence suggests that BDNF can increase axonal growth, but specific studies of mossy fiber sprouting, an example of axonal growth that may contribute to TLE, have not agreed that BDNF plays a key role. Most studies suggest that BDNF is not critical to mossy fiber sprouting (32,53,54), although other studies support a potential role (42,46,55).

An important point that may reconcile some of the disparities regarding the role that BDNF plays in epileptogenesis is that most of what is known about the actions of BDNF, to date, is based on studies that have used radically different preparations (e.g., brain region, animal age) and techniques. Furthermore, the results may not accurately reflect endogenous actions of BDNF because they are based on adding a pharmacologic concentration of recombinant BDNF to tissue. Little is known about the concentration of BDNF or proBDNF released in situ or whether it is always released synaptically. Our understanding of endogenous BDNF is, for the most part, inferred from anatomic or biochemical studies, but these studies typically use antibodies to BDNF or biochemical manipulations that are somewhat controversial. Thus, one antibody to BDNF has indicated that BDNF protein is transported anterogradely and packaged into dense core vesicles at synapses (9,56), but another antibody to BDNF suggests that BDNF expression is mainly somatic, and furthermore, BDNF expression can move from somata to dendrites after seizures (57).

Insights from Transgenic Mice

A great deal of information has come from the use of transgenic mice, particularly regarding the hypothesis that BDNF contributes to epileptogenesis and epilepsy. In knockout mice, homozygous deletions are lethal, so heterozygotes have been studied. In 1995, a seminal study showed that heterozygous knockouts have decreased seizure susceptibility and impaired kindling (58), providing a foundation for the hypothesis that BDNF is associated with epileptogenesis and epilepsy. The converse was evident in animals with BDNF overexpression, as increased seizure susceptibility and in vitro hyperexcitability occurred (59).

Subsequent studies of transgenic mice provided even more evidence that BDNF plays a role in seizure susceptibility, and perhaps, provided the first evidence of a role in epileptogenesis. These studies examined how two different transgenic lines responded to chemoconvulsants and subsequent development of spontaneous seizures. The first line, in which one of the truncated isoforms of trkB was overexpressed, was used to reduce the concentration of BDNF able to activate full-length trkB. However, given what is now known about truncated trkB, additional effects may have been present. Regardless, a remarkable effect was found on chronic seizures after kainic-acid–induced status epilepticus: spontaneous seizures were reduced, seizures were less severe, the onset of spontaneous seizures was delayed, and both mortality and interictal spiking were reduced (60). However, sample sizes were limited. Importantly, one of the reasons for this limitation was the inability to achieve status in animals with overexpressed truncated trkB, which in itself supports a role in seizures. The second transgenic line involved overexpression of full-length trkB. Surprisingly, converse effects to those found in the studies of the first transgenic line were not observed (61). Thus, chronic seizures were unaffected. However, severity of status epilepticus was increased by overexpression of full-length trkB, as was status-epilepticus–associated cell death, providing support for the overall hypothesis that the BDNF/trkB system is relevant to seizure susceptibility and associated neuronal damage.

These studies may have been confounded by developmental abnormalities that could have occurred in the CNS after perturbation of neurotrophins and their receptors during development of the transgenic mice, as well as by complex changes in neurotrophins and their receptors after seizures. A solution to this problem recently became available with the advent of conditional forebrain BDNF knockout animals, which have been used in the kindling model of epileptogenesis. Interestingly, the BDNF conditional knockout did not have severely altered kindling, arguing against the hypothesis for a critical role of BDNF in epileptogenesis (62). However, it was determined that trk was still phosphorylated in the BDNF knockouts, possibly by NT-3 or NT-4/5, making conclusions difficult. Fortuitously, a distinct transgenic line of mice, with conditional forebrain knockout of trkB, was made subsequently. In these animals, remarkably, kindling never occurred. However, prolonged afterdischarges were difficult to elicit, and this is important because afterdischarges are an essential initial step in kindling. Therefore, one could argue that this study primarily emphasizes a role of trkB in afterdischarges, and does so in a very compelling manner. In summary, the studies described above provide strong support for a role of neurotrophins acting at trkB receptors in seizures and epileptogenesis, but the precise role still needs to be defined.

Future Questions

Clearly, these studies suggest that developing AEDs that target trkB may be antiepileptogenic and anticonvulsant. It might be best not to forget, just yet, BDNF as a potential target, because a recent study showed that a polymorphism in the BDNF gene led to partial epilepsy (63). Moreover, brain tissue resected from patients with intractable TLE contains substantially elevated levels of BDNF (64,65), raising the possibility that if the excess could merely be decreased, seizures might be reduced. Indeed, reducing excess BDNF may actually aid cognitive function, which is often a problem in TLE, because overexpressing BDNF in mice appears to lead to deficits in learning and long-term potentiation (59). However, before such an approach can be seriously considered, a great deal more must be known about neurotrophins/trkB in the normal brain but, also, in the epileptic brain.

References

1. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem 2003;72:609–642.
2. Teng KK, Hempstead BL. Neurotrophins and their receptors: signaling trios in complex biological systems. Cell Mol Life Sci 2004;61:35–48.
3. Rose CR, Blum R, Pichler B, Lepier A, Kafitz KW, Konnerth A. Truncated TrkB-T1 mediates neurotrophin-evoked calcium signalling in glia cells. Nature 2003;426:74–78.
4. Chao MV, Bothwell M. Neurotrophins: to cleave or not to cleave. Neuron 2002;33:9–12.
5. Roux PP, Colicos MA, Barker PA, Kennedy TE. p75 Neurotrophin receptor expression is induced in apoptotic neurons after seizure. J Neurosci 1999;19:6887–6896.
6. Meyer A, Chretien P, Massicotte G, Sargent C, Chretien M, Marcinkiewicz M. Kainic acid increases the expression of the prohormone convertases furin and PC1 in the mouse hippocampus. Brain Res 1996;732:121–132.
7. Isackson PJ, Huntsman MM, Murray KD, Gall CM. BDNF mRNA expression is increased in adult rat forebrain after limbic seizures: temporal patterns of induction distinct from NGF. Neuron 1991;6:937–948.
8. Ernfors P, Bengzon J, Kokaia Z, Persson H, Lindvall O. Increased levels of messenger RNAs for neurotrophic factors in the brain during kindling epileptogenesis. Neuron 1991;7:165–176.
9. Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S. Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. J Neurosci 1997;17:2295–2313.
10. Humpel C, Wetmore C, Olson L. Regulation of brain-derived neurotrophic factor messenger RNA and protein at the cellular level in pentylenetetrazol-induced epileptic seizures. Neuroscience 1993;53:909–918.
11. Vezzani A, Ravizza T, Moneta D, Conti M, Borroni A, Rizzi M, Samanin R, Maj R. Brain-derived neurotrophic factor immunoreactivity in the limbic system of rats after acute seizures and during spontaneous convulsions: temporal evolution of changes as compared to neuropeptide Y. Neuroscience 1999;90:1445–1461.
12. Bengzon J, Kokaia Z, Ernfors P, Kokaia M, Leanza G, Nilsson OG, Persson H, Lindvall O. Regulation of neurotrophin and TrkA, TrkB and TrkC tyrosine kinase receptor messenger RNA expression in kindling. Neuroscience 1993;53:433–446.
13. Lindvall O, Kokaia Z, Bengzon J, Elmer E, Kokaia M. Neurotrophins and brain insults. Trends Neurosci 1994;17:490–496.
14. Merlio JP, Ernfors P, Kokaia Z, Middlemas DS, Bengzon J, Kokaia M, Smith ML, Siesjo BK, Hunter T, Lindvall O. Increased production of the TrkB protein tyrosine kinase receptor after brain insults. Neuron 1993;10:151–164.
15. Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. Nature 1995;373:109.
16. Sohrabji F, Miranda RC, Toran-Allerand CD. Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. Proc Natl Acad Sci U S A 1995;92:11110–11114.
17. Singh M, Meyer EM, Simpkins JW. The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague-Dawley rats. Endocrinology 1995;136:2320–2324.
18. Lohof AM, Ip NY, Poo MM. Potentiation of developing neuromuscular synapses by the neurotrophins NT-3 and BDNF. Nature 1993;363:350–353.
19. Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 1995;267:1658–1662.
20. Lu B, Gottschalk W. Modulation of hippocampal synaptic transmission and plasticity by neurotrophins. Prog Brain Res 2000;128:231–241.
21. Scharfman HE. Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. J Neurophysiol 1997;78:1082–1095.
22. Messaoudi E, Bardsen K, Srebro B, Bramham CR. Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus. J Neurophysiol 1998;79:496–499.
23. Marty S, Berzaghi M, Berninger B. Neurotrophins and activity-dependent plasticity of cortical interneurons. Trends Neurosci 1997;20:198–202.
24. Tanaka T, Saito H, Matsuki N. Inhibition of GABAA synaptic responses by brain-derived neurotrophic factor (BDNF) in rat hippocampus. J Neurosci 1997;17:2959–2966.
25. Frerking M, Malenka RC, Nicoll RA. Brain-derived neurotrophic factor (BDNF) modulates inhibitory, but not excitatory, transmission in the CA1 region of the hippocampus. J Neurophysiol 1998;80:3383–3386.
26. Rivera C, Li H, Thomas-Crusells J, Lahtinen H, Viitanen T, Nanobashvili A, Kokaia Z, Airaksinen MS, Voipio J, Kaila K, Saarma M. BDNF-induced TrkB activation down-regulates the K+-C1- cotransporter KCC2 and impairs neuronal C1- extrusion. J Cell Biol 2002;159:747–752.
27. Kovalchuk Y, Holthoff K, Konnerth A. Neurotrophin action on a rapid timescale. Curr Opin Neurobiol 2004;14:558–563.
28. Scharfman HE, Goodman JH, Sollas AL, Croll SD. Spontaneous limbic seizures after intrahippocampal infusion of brain-derived neurotrophic factor. Exp Neurol 2002;174:201–214.
29. Binder DK, Routbort MJ, Ryan TE, Yancpoulos GD, McNamara JO. Selective inhibition of kindling development by

intraventricular administration of TrkB receptor body. J Neurosci 1999;19:1424–1436.
30. Osehobo P, Adams B, Sazgar M, Xu Y, Racine RJ, Fahnestock M. Brain-derived neurotrophic factor infusion delays amygdala and perforant path kindling without affecting paired-pulse measures of neuronal inhibition in adult rats. Neuroscience 1999;92:1367–1375.
31. Larmet Y, Reibel S, Carnahan J, Nawa H, Marescaux C, Depaulis A. Protective effects of brain-derived neurotrophic factor on the development of hippocampal kindling in the rat. Neuroreport 1995;6:1937–1941.
32. Xu B, Michalski B, Racine RJ, Fahnestock M. The effects of brain-derived neurotrophic factor (BDNF) administration on kindling induction, Trk expression and seizure-related morphological changes. Neuroscience 2004;126:521–531.
33. Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing? Trends Neurosci 2001;24:47–53.
34. Kim YH, Rhyu IJ, Park KW, Eun BL, Kim YI, Rha HK, Kim DS, Jo YH, Whang KT, Kim MS. The induction of BDNF and c-fos mRNA in the hippocampal formation after febrile seizures. Neuroreport 2001;12:3243–3246.
35. Chou IC, Tsai CH, Lee CC, Lin SS, Tsai FJ. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in febrile seizures. Epilepsy Res 2004;60:27–29.
36. Gilmore JH, Jarskog LF, Vadlamudi S. Maternal infection regulates BDNF and NGF expression in fetal and neonatal brain and maternal-fetal unit of the rat. J Neuroimmunol 2003;138:49–55.
37. Tabakman R, Lecht S, Sephanova S, Arien-Zakay H, Lazarovici P. Interactions between the cells of the immune and nervous system: neurotrophins as neuroprotection mediators in CNS injury. Prog Brain Res 2004;146:387–401.
38. Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron 1992;9:1081–1088.
39. Lahteinen S, Pitkanen A, Knuuttila J, Toronen P, Castren E. Brain-derived neurotrophic factor signaling modifies hippocampal gene expression during epileptogenesis in transgenic mice. Eur J Neurosci 2004;19:3245–3254.
40. Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 2002;82:1367–1375.
41. Scharfman HE, Goodman JH, Macleod A, Phani S, Antonelli C, Croll SD. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 2004 (in press).
42. Danzer SC, Crooks KR, Lo DC, McNamara JO. Increased expression of brain-derived neurotrophic factor induces formation of basal dendrites and axonal branching in dentate granule cells in hippocampal explant cultures. J Neurosci 2002;22:9754–9763.
43. Horch HW, Kruttgen A, Portbury SD, Katz LC. Destabilization of cortical dendrites and spines by BDNF. Neuron 1999;23:353–364.
44. Murphy DD, Cole NB, Segal M. Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. Proc Natl Acad Sci U S A 1998;95:11412–11417.
45. Tyler WJ, Pozzo-Miller L. Miniature synaptic transmission and BDNF modulate dendritic spine growth and form in rat CA1 neurones. J Physiol 2003;553:497–509.
46. Lowenstein DH, Arsenault L. Dentate granule cell layer collagen explant cultures: spontaneous axonal growth and induction by brain-derived neurotrophic factor or basic fibroblast growth factor. Neuroscience 1996;74:1197–1208.
47. Swann JW, Al-Noori S, Jiang M, Lee CL. Spine loss and other dendritic abnormalities in epilepsy. Hippocampus 2000;10:617–625.
48. Ribak CE, Dashtipour K. Neuroplasticity in the damaged dentate gyrus of the epileptic brain. Prog Brain Res 2002;136:319–328.
49. Scharfman HE. Functional implications of seizure-induced neurogenesis. Adv Exp Med Biol 2004;548:192–212.
50. Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. Trends Neurosci 1999;22:25–30.
51. Yano H, Chao MV. Mechanisms of neurotrophin receptor vesicular transport. J Neurobiol 2004;58:244–257.
52. Drakew A, Muller M, Gahwiler BH, Thompson SM, Frotscher M. Spine loss in experimental epilepsy: quantitative light and electron microscopic analysis of intracellularly stained CA3 pyramidal cells in hippocampal slice cultures. Neuroscience 1996;70:31–45.
53. Qiao X, Suri C, Knusel B, Noebels JL. Absence of hippocampal mossy fiber sprouting in transgenic mice overexpressing brain-derived neurotrophic factor. J Neurosci Res 2001;64:268–276.
54. Bender R, Heimrich B, Meyer M, Frotscher M. Hippocampal mossy fiber sprouting is not impaired in brain-derived neurotrophic factor-deficient mice. Exp Brain Res 1998;120:399–402.
55. Koyama R, Yamada MK, Fujisawa S, Katoh-Semba R, Matsuki N, Ikegaya Y. Brain-derived neurotrophic factor induces hyperexcitable reentrant circuits in the dentate gyrus. J Neurosci 2004;24:7215–7224.
56. Fawcett JP, Aloyz R, McLean JH, Pareek S, Miller FD, McPherson PS, Murphy RA. Detection of brain-derived neurotrophic factor in a vesicular fraction of brain synaptosomes. J Biol Chem 1997;272:8837–8840.
57. Tongiorgi E, Armellin M, Giulianini PG, Bregola G, Zucchini S, Paradiso B, Steward O, Cattaneo A, Simonato M. Brain-derived neurotrophic factor mRNA and protein are targeted to discrete dendritic laminas by events that trigger epileptogenesis. J Neurosci 2004;24:6842–6852.
58. Kokaia M, Ernfors P, Kokaia Z, Elmer E, Jaenisch R, Lindvall O. Suppressed epileptogenesis in BDNF mutant mice. Exp Neurol 1995;133:215–224.
59. Croll SD, Suri C, Compton DL, Simmons MV, Yancopoulos GD, Lindsay RM, Wiegand SJ, Rudge JS, Scharfman HE. Brain-derived neurotrophic factor transgenic mice exhibit passive avoidance deficits, increased seizure severity and in vitro hyperexcitability in the hippocampus and entorhinal cortex. Neuroscience 1999;93:1491–1506.
60. Lahteinen S, Pitkanen A, Saarelainen T, Nissinen J, Koponen E, Castren E. Decreased BDNF signalling in transgenic mice reduces epileptogenesis. Eur J Neurosci 2002;15:721–734.
61. Lahteinen S, Pitkanen A, Koponen E, Saarelainen T, Castren E. Exacerbated status epilepticus and acute cell loss, but no changes in epileptogenesis, in mice with increased brain-derived neurotrophic factor signaling. Neuroscience 2003;122:1081–1092.

62. He XP, Kotloski R, Nef S, Luikart BW, Parada LF, McNamara JO. Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. Neuron 2004;43:31–42.
63. Kanemoto K, Kawasaki J, Tarao Y, Kumaki T, Oshima T, Kaji R, Nishimura M. Association of partial epilepsy with brain-derived neurotrophic factor (BDNF) gene polymorphisms. Epilepsy Res 2003;53:255–258.
64. Mathern GW, Babb TL, Micevych PE, Blanco CE, Pretorius JK. Granule cell mRNA levels for BDNF, NGF, and NT-3 correlate with neuron losses or supragranular mossy fiber sprouting in the chronically damaged and epileptic human hippocampus. Mol Chem Neuropathol 1997;30:53–76.
65. Murray KD, Isackson PJ, Eskin TA, King MA, Montesinos SP, Abraham LA, Roper SN. Altered mRNA expression for brain-derived neurotrophic factor and type II calcium/calmodulin-dependent protein kinase in the hippocampus of patients with intractable temporal lobe epilepsy. J Comp Neurol 2000;418:411–422.