

DOES BDNF CONTRIBUTE TO TEMPORAL LOBE EPILEPSY?

Brain-Derived Neurotrophic Factor Enhances Fast Excitatory Synaptic Transmission in Human Epileptic Dentate Gyrus

Zhu WJ, Roper SN

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PURPOSE: Brain-derived neurotrophic factor (BDNF) has trophic effects and modulates synaptic transmission in the hippocampal formation in animal studies. It also is upregulated in acute and chronic epilepsy models and in human temporal lobe epilepsy. This study was undertaken to examine the effects of BDNF on fast synaptic transmission in the human epileptic dentate gyrus.

METHODS: Hippocampal specimens were acquired from patients with temporal lobe epilepsy during surgical removal of the anterior temporal lobe, intended to treat the epileptic condition. Whole-cell patch-clamp recordings were obtained from dentate granule cells in transverse hippocampal slices *in vitro*.

RESULTS: Application of BDNF increased the amplitude and frequency of spontaneous excitatory postsynaptic currents and increased the amplitude of evoked excitatory postsynaptic currents. BDNF had no effect on spontaneous inhibitory postsynaptic currents but produced a decrease in amplitude of evoked inhibitory postsynaptic currents. The effects of BDNF were abolished by coapplication of the tyrosine kinase inhibitor K252a; therefore, BDNF enhances fast excitatory transmission in the epileptic human dentate gyrus and may play an important role in epileptogenesis in temporal lobe epilepsy.

CONCLUSIONS: This raises the possibility of designing therapies for this disorder that may be both anticonvulsant and antiepileptogenic.

COMMENTARY

Studies over the past decade have demonstrated novel roles for the neurotrophin family in the adult brain, and perhaps the most intriguing, and the one with the most implications, is the ability to potentiate glutamatergic synaptic trans-

mission. One of the neurotrophins, brain-derived neurotrophic factor (BDNF), has received much attention because it is highly expressed in many areas of the brain that are thought to be involved in limbic seizures; indeed it is perhaps no coincidence that BDNF-immunoreactive fibers innervate the regions most vulnerable in temporal lobe epilepsy (1,2).

The first evidence that BDNF enhanced transmission in the adult brain were experiments in rat hippocampal slices. It was shown that BDNF application led to a long-lasting potentiation of synaptic transmission in area CA1 (3). Subsequently it was shown that similar effects occurred in other parts of the trisynaptic circuit (4–6), although not in all cases, and indeed some laboratories have failed to replicate these results. The effects that have been described appear to be mediated by the BDNF high-affinity receptor, *trkB*. Subsequent studies demonstrated additional effects of BDNF in hippocampus, such as decreased γ -aminobutyric acid (GABA)ergic transmission (7,8), phosphorylation of *N*-methyl-d-aspartate (NMDA) receptors (9,10), and actions at sodium channels (11). Thus although all effects of BDNF are consistent with increased excitability, the precise mechanisms and locus of the actions of BDNF are controversial (12).

Although much of the literature has focused on the actions of BDNF in the normal hippocampus, several articles have indicated a role of BDNF in seizures and, possibly, epileptogenesis (for review, see 13). Thus transgenic mice with decreased BDNF have a higher seizure threshold (14), and overexpression of BDNF facilitates seizures (15). Infusion of a BDNF scavenger into the hilar region of the dentate gyrus impairs kindling (16), and infusion of BDNF into hippocampus is followed by seizures (17). The *in vivo* studies have not all been in agreement, however, because prolonged infusion of BDNF into the hilus was shown to delay kindling (18,19). Complex temporal changes in *trk* receptors after prolonged BDNF exposure could have contributed to these results (20), but it also was suggested that the delay in kindling was mediated by a BDNF-induced increase in neuropeptide Y (NPY) (21,22), an intriguing possibility, given that NPY has been shown to depress synaptic transmission in hippocampus (23).

Particularly interesting is the evidence that BDNF expression increases after seizures (24) and after other insults as well (25). The increase in expression after seizures is extremely robust, having been described by many different laboratories, in

which diverse animal models of epilepsy were used. The increased expression of BDNF after seizures suggests positive feedback that might support the development of chronic seizures (i.e., epilepsy) (13). New evidence from human tissue resected from intractable epileptics now shows that BDNF expression and action in human tissue are consistent with those in the rat, supporting the hypothesis that BDNF may play a role in human temporal lobe epilepsy (TLE). Thus granule cells strongly express BDNF (26), and in tissue from patients with intractable TLE, BDNF expression in granule cells increases (26,27).

Besides the localization studies, the Roper laboratory has shown in hippocampal slices from TLE patients that BDNF exposure potentiates granule cell excitation and impairs granule cell inhibition (28). Granule cells of the dentate gyrus were patch-clamped to examine the effects of BDNF application on spontaneous and evokes excitatory postsynaptic currents (EPSCs) and inhibitory PSCs (IPSCs). Both the amplitude and frequency of spontaneous EPSCs were increased; evoked EPSC amplitude also was increased, and there was a decrease in amplitude of evoked IPSCs. This work strongly supports a role of BDNF in human epilepsy and raises the possibility that interference with BDNF expression or BDNF action may be a therapeutic strategy for treating epilepsy.

Although it is certainly worth consideration, can an anti-convulsant that interferes with the actions of BDNF succeed? Given that BDNF may normally play a role in cognitive functions such as learning and memory and be important to the developing nervous system of children with epilepsy, side effects would seem to be a substantial potential problem, yet the problem may not be insurmountable. One reason is that BDNF expression appears to be higher in the brain of those with epilepsy than normal individuals. Thus one might be able to use an antagonist to decrease the effects of abnormally high BDNF without impairing normal functions that require relatively low levels of BDNF. Another approach would be to interfere with the molecular machinery that controls BDNF transcription and translation (29), without blocking trkB-receptor function at all. This strategy could potentially blunt the seizure-induced increase in BDNF expression (i.e., the positive feedback described earlier), which may contribute to and even perpetuate the epileptic state. What is critical to this field is the development of suitable pharmacologic tools to test these hypotheses, which will allow us to determine whether impairing BDNF/trkB signaling is a possible therapy for TLE.

by Helen Scharfman, Ph. D.

References

- 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.
- Yan Q, Rosenfeld RD, Matheson CR, Hawkins N, Lopez OT, Bennett L, Welcher AA. Expression of brain-derived neurotrophic factor protein in the adult rat central nervous system. *Neuroscience* 1997; 78:431–448.
- Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science* 1995;267:1658–1662.
- Scharfman HE. Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. *J Neurophysiol* 1997;78:1082–1095.
- Messaoudi E, Bardsen K, Srebro B, Bramham CR. Acute intrahippocampal infusion of brain-derived neurotrophic factor induces lasting potentiation of synaptic transmission in the rat dentate gyrus. *J Neurophysiol* 1998;9:496–499.
- Asztely F, Kokaia M, Olofsson K, Ortegren U, Lindvall O. Afferent-specific modulation of short-term synaptic plasticity by neurotrophins in dentate gyrus. *Eur J Neurosci* 2000;12:662–669.
- Tanaka T, Saito H, Matsuki N. Inhibition of GABA synaptic responses by brain derived neurotrophic factor (BDNF) in rat hippocampus. *J Neurosci* 1997.
- 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.
- Suen PC, Wu K, Levine ES, Mount HTJ, Xu JL, Black SYLB. Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic N-methyl-D-aspartate receptor subunit 1. *Proc Natl Acad Sci U S A* 1997;94:8191–8195.
- Lin SY, Wu K, Levine ES, Mount HTJ, Suen PC, Black IB. BDNF rapidly enhances tyrosine phosphorylation of NMDA receptor subunit 2B in postsynaptic densities of rat cerebral cortex and hippocampus. *Mol Brain Res* 1998;55:20–27.
- Kaffitz KW, Rose CR, Thoenen H, Konnerth A. Neurotrophin-evoked rapid excitation through trkB receptors. *Nature* 1999;401:918–921.
- Manabe T. Does BDNF have pre- or postsynaptic targets? *Science* 2002;295:1651–1653.
- Binder D, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing? *Trends Neurosci* 2001;24:47–53.
- Kokaia M, Enfors P, Kokaia Z, Elmer E, Jaenisch R, Lindvall O. Suppressed epileptogenesis in BDNF mutant mice. *Exp Neurol* 1995; 133:215–224.
- Croll SD, Suri C, Compton DL, Simmons MV, Yancopoulos GD, Lindsay RM, Wiegand SJ, Scharfman HE. Brain-derived neurotrophic factor (BDNF) transgenic mice exhibit passive avoidance deficits, increased seizure severity and in vitro hyperexcitability in the hippocampus and entorhinal cortex. *Neuroscience* 1999;93:1491–1506.
- Binder DK, Routbort MJ, Ryan TE, Yancopoulos GD, McNamara JO. Selective inhibition of kindling development by intraventricular administration of trkB receptor body. *J Neurosci* 1999;19:1424–1436.
- Scharfman H, Goodman J, Sollas A, Croll S. Spontaneous limbic seizures after intrahippocampal infusion of brain-derived neurotrophic factor (BDNF). *Exp Neurol* (in press).
- Larmer 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.
- Osehobo P, Adams B, Sazgar M, Xu Y, Racine R, Fahnestock M. Brain-derived neurotrophic factor infusion delays amygdala and per-

- forant path kindling without affecting paired pulse measures of neuronal inhibition in adult rats. *Neuroscience* 1999;92:1367–1375.
20. Rudge JS, Mather PE, Pasnikowski EM, Ning C, Corcoran T, Acheson A, Anderson K, Lindsay RM, Wiegand SJ. Endogenous BDNF protein is increased in adult rat hippocampus after a kainic acid induced excitotoxic insult but exogenous BDNF is not neuroprotective. *Exp Neurol* 1998;149:398–410.
 21. Croll SD, Wiegand SJ, Anderson KD, Lindsay RM, Nawa H. Regulation of neuropeptides in adult rat forebrain by the neurotrophins BDNF and NGF. *Eur J Neurosci* 1994;6:1343–1353.
 22. Reibel S, Larmet Y, Carnahan J, Marescaux C, Depaulis A. Endogenous control of hippocampal epileptogenesis: a molecular cascade involving brain derived neurotrophic factor and neuropeptide Y. *Epilepsia* 2000;41:S127–S133.
 23. Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. *Trends Neurosci* 1999;2:25–30.
 24. Gall C, Lauterborn J, Isackson P, White J. Seizures, neuropeptide regulation and mRNA expression in the hippocampus. *Prog Brain Res* 1990;83:371–390.
 25. Lindvall O, Kokaia Z, Bengzon J, Elmer E, Kokaia M. Neurotrophins and brain insults. *Trends Neurosci* 1994;17:490–496.
 26. Murray K, Isackson P, Eskin T, King M, Montesinos S, Abraham L, Roper S. 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.
 27. 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.
 28. Zhu W, Roper S. Brain-derived neurotrophic factor enhances fast excitatory synaptic transmission in human epileptic dentate gyrus. *Ann Neurol* 2001;50:188–194.
 29. Murray K, Hayes V, Gall C, Isackson P. Attenuation of the seizure-induced expression of BDNF mRNA in adult rat brain by an inhibitor of calcium/calmodulin-dependent protein kinases. *Eur J Neurosci* 1998;10:377–387.