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Cutting through the complexity: the role of brain-derived neurotrophic factor in post-traumatic epilepsy (Commentary on Gill *et al.*)

Helen E. Scharfman

The Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA

Brain-derived neurotrophic factor (BDNF) is one of the most avidly discussed molecules in neuroscience because of its diverse roles in development and plasticity. For this reason, there are many diseases of the central nervous system that have implicated a disruption in the normal actions of BDNF in the underlying etiology. One disease where BDNF appears to play a very important but complex role is epilepsy, especially post-traumatic epilepsy, where an injury leads to epilepsy. BDNF has been implicated in the development of epilepsy after injury (epileptogenesis) for many reasons, such as its influence on the maladaptive plastic processes that occur during epileptogenesis ('pathological plasticity'). A central question remains: are the effects of BDNF causal, i.e. do they contribute to epileptogenesis, or are they compensatory, and protect the brain from epilepsy? Today there is still no clear answer, although Gill *et al.* (2013) provide an important piece of evidence that, at least in the hippocampus, BDNF contributes to epileptogenesis. Moreover, they show that the effects are due to a facilitation of the abnormal rewiring of brain circuitry after injury, and the promotion of hyperexcitability.

The authors used an elegant model system, i.e. organotypic cultures, to their advantage. In this preparation, a lesion can be made that is fairly reproducible from culture to culture. Clinical studies do not have this 'luxury,' and continue to present a puzzling picture, possibly for this reason, i.e. only a subset of individuals with brain injury develop epilepsy.

Gill *et al.* (2013) followed the consequences of their specific lesion, to the Schaffer collaterals, with several measurements. First, they monitored axonal rewiring with anatomical methods. Second, they recorded from the neurons of origin of the Schaffer collaterals, the pyramidal cells in area CA3. The results showed robust axonal sprouting and increased action potential discharge in CA3 pyramidal cells after lesions. Remarkably, both effects were blocked by a commonly used scavenger of BDNF, TrkB-Fc. This molecule combines IgG with the recognition site for BDNF at its receptor TrkB. Importantly, it is possible that TrkB-Fc also scavenges neurotrophin-4/5, another neurotrophin that binds to TrkB (see He *et al.*, 2004), but there are arguments that neurotrophin-4/5 is not critical, at least in the kindling model of epilepsy (He *et al.*, 2006).

One would think that the experiments of Gill *et al.* (2013) would lead to preclinical tests of compounds like TrkB-Fc to reduce the aberrant sprouting and hyperexcitability after brain injury, and therefore block epilepsy. However, it is unfortunately not clear that such a strategy would work clinically – at least not yet. For example, the role of BDNF may not be the same for all types of injury. In the dentate gyrus, one form of axonal sprouting that has been examined in the context of epilepsy is mossy fiber sprouting, which refers to the reorganization of granule cell axons. In previous studies, BDNF has been implicated in mossy fiber sprouting (Tamura *et al.*, 2009). However, mossy fiber sprouting does not always depend on BDNF (Kokaia *et al.*, 1995; Bender *et al.*, 1998; Qiao *et al.*, 2001) and, in some published reports, BDNF appears to inhibit sprouting (Hattiangady *et al.*, 2006; Paradiso *et al.*, 2011). In addition, although granule cell hyperexcitability develops in animal models of epilepsy with mossy fiber sprouting and is promoted by BDNF (Scharfman *et al.*, 1999), there is also hyperinhibition of granule cells (Harvey & Sloviter, 2005).

Another topic that is relevant to the role of BDNF in post-traumatic epilepsy is neocortical injury, which also leads to local hyperexcitability and seizures, but BDNF is protective (Prince *et al.*, 2009). In these studies, BDNF appears to protect GABAergic neurons and, as a result, maintains inhibitory control of network excitability (Prince *et al.*, 2009).

Indeed, it has been suggested that BDNF is a ‘double-edged sword’ (Binder *et al.*, 2001). For example, adding BDNF to a slice from an epileptic rat causes spontaneous burst discharges (Scharfman *et al.*, 1999) but it also induces the synthesis of neuropeptide Y, which has anticonvulsant actions (Sperk *et al.*, 2007; Scharfman & MacLusky, 2008). These data are consistent with the findings that infusion of BDNF into the hippocampus of normal adult rats triggers seizures, but seizures do not persist (Scharfman *et al.*, 2002). Nevertheless, the studies of Gill *et al.* (2013) make excellent use of an experimental test-bed to ask more about this ‘double-edged sword’ that describes the actions of BDNF in epilepsy, and to find a way to make it a ‘single-edged blade.’

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