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Commentary

Environmental enrichment: Evidence for an unexpected therapeutic influence

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ABSTRACT

Environmental enrichment produces wide-ranging effects in the brain at molecular, cellular, network, and behavioral levels. The changes in neuronal plasticity are driven by changes in neurotransmitters, neurotrophic factors, neuronal morphology, neurogenesis, network properties of the brain, and behavioral correlates of learning and memory. Exposure to an enriched environment has also demonstrated intriguing possibilities for treatment of a variety of neurodegenerative diseases including Huntington's disease, Alzheimer's disease, and Parkinson's disease. The effect of environmental enrichment in epilepsy, a neurodegenerative disorder with pathological neuronal plasticity, is of considerable interest. Recent reports of the effect of environmental enrichment in the *Bassoon* mutant mouse, a genetic model of early onset epilepsy, provides a significant addition to the literature in this area.

Introduction

The epilepsies are a diverse group of neurological disorders defined by an unprovoked seizure and a brain which has an enduring predisposition to seizures (Fisher et al., 2014). In a recent issue of Experimental Neurology, Morelli et al. (2014) report on an electrophysiological and morphological analysis of the effects of environmental enrichment on the development and expression of epilepsy in mice with a mutation in the presynaptic protein *Bassoon*. They provide evidence that environmental enrichment influences functional and structural features of neural circuitry associated with epilepsy and its development in this model of epilepsy. The results of the study add to evidence that environmental experience can modify development and expression of a variety of disorders in the nervous system, and offer an intriguing clue about the powerful effects of environment on the structure and function of neural circuits.

Epilepsy is estimated to have a lifetime incidence of up to 5 per 1000 in developed countries and 2–3 fold greater in developing countries and affects nearly 70 million people worldwide (Ngugi et al., 2010). The impact of seizures in epilepsy has a magnified effect on the quality of life of those affected due to the unpredictability of the seizures, which can result in serious injury, limits activities, and often precludes driving. Epilepsy is also associated with significant social stigma, which can further limit employment and social interactions (Jacoby and Austin, 2007). Furthermore, cognitive deficits and mental health disorders are frequently seen as co-morbidities with epilepsy (LaFrance et al., 2008). Current pharmacological therapies fail to control seizures in 25–30% of individuals (Kwan and Brodie, 2000; Mattson et al., 1996), and despite the introduction of several new anti-seizure medications, some with novel mechanisms of action, the proportion of medically intractable cases has not changed (Boon et al., 2002; Cross and Riney, 2009; Leppik, 2002; Matsuo and Riaz, 2009). Additionally, pharmacologic anti-seizure medications are known to have a variety of significant adverse effects (Swann, 2001), including impairing cognitive functioning (Park and Kwon, 2008). Therefore significant effort is appropriately directed toward the identification of novel therapeutic approaches, including non-pharmacological approaches, for epilepsy.

Commonly the recurrent seizures of epilepsy are associated with a progressive neurodegenerative process. One of the most common forms of epilepsy in humans, temporal lobe epilepsy (TLE), has been demonstrated in numerous studies of humans and in animal models to be associated with the progressive development of structural and functional pathologies. Continued seizures in TLE are associated with progressive worsening of seizures (French et al., 1993), increasing resistance to anti-seizure medications (Kwan and Brodie, 2000), progressive damage to the hippocampus, amygdala, and entorhinal cortex (Bernasconi et al., 2005), as well as more wide-spread cerebral atrophy (Bernhardt et al., 2009). Neuropsychological deficits are more significant in those with a greater duration of TLE (Oyegbile et al., 2004). Animal studies utilizing various models of TLE have demonstrated cell

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death (Kotloski et al., 2002), development of aberrant connections including sprouting of mossy fibers, dentate granule cells (Cavazos et al., 1991), CA3 neurons (Siddiqui and Joseph, 2005), entorhinal cortex (Shetty, 2002), and anomalous migration of new cells (Houser, 1990; Parent et al., 1997) which progress with repeated seizures. Worsening deficits in learning and memory have also been demonstrated with an increasing number of seizures in a rat model of TLE (Kotloski et al., 2002).

While a significant proportion of those with TLE may have effective control of their seizures with medications, adverse side effects are common with many of these medications. For those whose seizures are pharmaco-resistant, surgical resection of the seizure focus may lead to control of the seizures, though surgical resection may also result in significant cognitive deficits (Spencer and Huh, 2008). Finally, a significant number of individuals are unable to control their seizures with either medications or surgery and they continue to suffer from chronic recurrent seizures. Additional therapeutic approaches are needed for these individuals.

Environmental enrichment in animals

Environmental enrichment has been demonstrated to have a beneficial impact in a variety of neurodegenerative diseases such as Alzheimer's disease (Jankowsky et al., 2005; Lazarov et al., 2005), Parkinson's disease (Faherty et al., 2005; Jadavji et al., 2006), and Huntington's disease (van Dellen et al., 2000), as well as in traumatic brain injury (Frasca et al., 2013; Kovesdi et al., 2011; Miller et al., 2013), the effect of environmental enrichment in epilepsy is an intriguing area of research. The impact of environmental enrichment was recognized by Donald Hebb more than sixty years ago. Hebb found that rats kept in his home as pets had superior behavioral performance to rats maintained in standard laboratory housing (Hebb, 1947). Hebb later developed early theories of synaptic plasticity as the basis of learning (Hebb, 1949), a concept central to our current understanding of environmental enrichment. Over the intervening decades, paradigms of environmental enrichment have developed to include increased numbers of cage-mates, larger cages with objects varying in color and texture that are changed over time, as well as tunnels and running wheels. Standardized enriched housing has also been proposed (Fares et al., 2013). These modifications result in greater social interaction, cognitive stimulation, spatial learning, and motor activity for the animals, which may be closer to a natural environment for the animals than standard laboratory housing conditions.

Environmental enrichment has been demonstrated to have effects on the brain at genetic, molecular, cellular, network, and behavioral levels. Expression of immediate early genes including *NGFI-A/Zif268* (Wallace et al., 1995) and *Arc* (Pinaud et al., 2001) is increased by an enriched environment, while the cyclic AMP response element binding protein (CREB) demonstrates increased phosphorylation (Young et al., 1999). An enriched environment was associated with increased levels of glia-derived neurotrophic factor (GDNF) (Young et al., 1999), brain-derived neurotrophic factor (BDNF) (Branchi et al., 2006; Young et al., 1999), nerve growth factor (NGF) (Branchi et al., 2006; Pham et al., 1999), neurotrophin-3 (NT-3) (Torasdotter et al., 1996), insulin-like growth factor (IGF-1) (Carro et al., 2001), and vascular endothelial growth factor (VEGF) (Bengoetxea et al., 2008; During and Cao, 2006). Furthermore many neurotransmitter systems, including glutamatergic (Bredy et al., 2004; Foster et al., 1996; Naka et al., 2005; Segovia et al., 2006), GABAergic (Segovia et al., 2006), cholinergic (Del Arco et al., 2007; Rosenzweig and Bennett, 1996), dopaminergic (Bowling et al., 1993), and serotonergic (Rasmuson et al., 1998), are impacted by environmental enrichment. These wide-spread changes resulting from environmental enrichment should not be unexpected in an organ tasked with assessing and responding to the external environment.

At a cellular level, an enriched environment has been shown to induce increases in the size of neuronal soma (Faherty et al., 2003), and to increase the numbers of dendritic branches (Fiala et al., 1978; Greenough et al., 1973), spines (Globus et al., 1973), and synapses (West and Greenough, 1972). Levels of post-synaptic density-95 (PSD-95) gene expression (Rampon et al., 2000a) and protein (He et al., 2010; Nithianantharajah et al., 2004) increase in an enriched environment. Enhanced synaptic strength (Foster and Dumas, 2001; Green and Greenough, 1986) and increased glutamatergic transmission (He et al., 2010; Melendez et al., 2004; Naka et al., 2005) have been shown following environmental enrichment. Long-term potentiation (LTP) in hippocampal slices is enhanced following exposure to an enriched environment (Artola et al., 2006; Duffy et al., 2001). Furthermore, neurogenesis in the hippocampus (Kempermann et al., 1997; Young et al., 1999), decreased apoptosis (Young et al., 1999), and increased numbers of non-neuronal cells (Altman and Das, 1964; Walsh et al., 1969) also are induced by an enriched environment. Increased neurogenesis has been linked to improved learning and memory (Bruel-Jungerman et al., 2005; Kempermann et al., 2002), as well as the behavioral effects of some anti-depressants (Santarelli et al., 2003; Surget et al., 2008).

Improvements in learning and memory resulting from an enriched environment include improvement in performance of the Morris water maze (Dahlqvist et al., 2004; Jankowsky et al., 2005; Kempermann et al., 1997; Mohammed et al., 1990), the radial arm maze (Bindu et al., 2005; Dhanushkodi et al., 2007), and hippocampal-independent tasks such as novel object recognition (Rampon et al., 2000b).

Environmental enrichment in humans

For humans, an enriched environment in the form of a higher level of educational attainment has been associated with a reduced risk of Alzheimer's (Snowdon et al., 1996) and Parkinson's disease-related dementia (Glatt et al., 1996). For epilepsy, enhanced vigilance may inhibit seizures (Vieth, 1986). Increased exercise, which may be considered another aspect of the enriched environment, was shown to decrease seizure frequency in several studies (Jalava and Sillanpaa, 1997; Roth et al., 1994; Steinhoff et al., 1996) including one prospective study (Eriksen et al., 1994), although no effect of exercise on seizure frequency was found in two other studies (McAuley et al., 2001; Nakken et al., 1990).

Environmental enrichment and epilepsy

As environmental enrichment has shown clinical utility in several neurodegenerative conditions and as some forms of epilepsy may also be considered a neurodegenerative process, environmental enrichment is an attractive potential therapeutic approach for epilepsy. Furthermore, as epilepsy is at least in part due to a pathological plasticity, a therapeutic approach based on healthy plasticity is intriguing. Conceptually, the effects of enriched environment on epilepsy could be divided into prevention (i.e. susceptibility to an initial epileptogenic insult) and treatment (i.e. anti-seizure effects in an epileptic animal). Work done by Young et al. (1999) demonstrated that housing in an enriched environment protected rats from the development of kainic acid-induced seizures and status epilepticus. Furthermore, when rats were given a suprathreshold dose of kainic acid to induce status epilepticus and when the duration of status epilepticus was equivalent among animals, rats housed in an enriched environment demonstrated substantially reduced cell death in the dentate hilus and CA3 regions, as compared to rats housed in a standard environment. Auvergne et al. (2002) demonstrated that amygdala kindling was delayed in rats housed in an enriched environment for four weeks prior to the start of kindling, although rats placed into an enriched environment at the onset of the kindling procedure did not differ in kindling epileptogenesis from rats housed in standard conditions. However neurogenesis within the dentate granule cell layer was elevated and equivalent in the two groups housed in an enriched environment, as compared to standard