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REVIEW ARTICLE

DOES ENVIRONMENTAL ENRICHMENT THWART TEMPORAL LOBE EPILEPSY AND CO-MORBIDITIES IN AGED SUBJECTS?

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ABSTRACT

Epilepsy is widely prevalent in the elderly populations. Besides unpredictable seizure attacks, co-morbidities like cognitive impairment, anxiety, depression and disturbed social behavior are severe in elderly subjects inflicted with epilepsy. Though anti- epileptic drugs (AED) are the most common means of treating TLE, undesirable side effects associated with them limit their usage. Thus, there is a pressing need to develop alternative non-invasive therapeutic strategies to treat elderly individuals with TLE. Environmental enrichment (EE) has been shown to be beneficial in immature and young epileptic rats. However, knowledge regarding the effects of EE in aged epileptic subjects has not garnered much attention. As aging is one of the predominant risk factor involved in seizure development, a non-invasive therapeutic alternative like EE for treating elderly patients with TLE will be extremely beneficial. The proposed hypotheses suggest possible non-invasive therapeutic approaches to mitigate hippocampal abnormalities, epileptogenesis and co-morbidities in aged subjects with TLE. This kind of study would shed light on the cellular and molecular basis underlying anti-epileptic and cognition enhancing effects of enriched rehabilitation for treating drug resistant TLE in young as well as aged subjects.

INTRODUCTION

Temporal lobe epilepsy (TLE) is a devastating disease. Besides unpredictable seizure attacks, TLE patients also suffer from co-morbidities like cognitive impairment, depression, anxiety and problems with social behavior (Babu *et al*., 2009; Jacobs *et al*., 2009). Based on pre-clinical and clinical observations, it is evident that the hippocampus undergoes massive alteration following status epilepticus (SE) that sets a conducive environment for the development of chronic epilepsy or TLE (Parent and Kron 2012; Rao *et al*., 2006). In contrast to SE, TLE results in a significant decrease in hippocampal neurogenesis that correlates with cognitive dysfunction and co-morbidities like depression. The magnitude of TLE related suffering is several folds higher in elderly subjects (Sanya 2010). The declined neurogenesis observed in TLE, which is more prominent in elderly subjects, is attributable to age related decrease in trophic factor support (Kuruba *et al*., 2009). On the other hand, enriched environment (EE) has been shown to increase hippocampal neurogenesis, neurotrophic factor levels and cognitive functions in naïve rodents (Dhanushkodi and Shetty 2008; Faverjon *et al*., 2002; Harati *et al*., 2011; Nithianantharajah and Hannan, 2006). As a proof of principle, several studies have shown the anti-epileptic and cognition enhancing effects of EE in immature and young rodents. (Auvergne *et al*., 2002; Faverjon *et al*., 2002; Koh *et al*., 2005; Koh *et al*., 2007; Korbey *et al*., 2008; Manno *et al*., 2011; Rutten *et al*., 2002; Stewart *et al*., 2012; Xie *et al*., 2012; Young *et al*., 1999). However, the anti-epileptogenic and cognition enhancing role of EE in aged subjects experiencing acute seizures or chronic epilepsy (TLE) is unknown. As the proportion of aged population is increasing globally and aging being one of the pre-disposing factors for seizure sensitivity and severity, there is a pressing need to identify non-invasive therapeutic approaches like EE, for preventing and rehabilitating elderly subjects with epilepsy. Furthermore, it is also important to have an in-depth analysis of the mechanisms underlying anti-epileptic and cognition enhancing effects of EE.

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Aging and epilepsy

Epilepsy is highly prevalent in the elderly populations and is one of the most common neurological disorders after stroke and dementia. Aged populations are more prone to epilepsy owing to age related decrease in inhibitory transmission, neurotrophic factor levels and dysfunctional endogenous anti-epileptic mechanisms. Epilepsy is typically characterized by unpredictable occurrence of seizures due to an imbalance in excitatory and inhibitory activities between the brain structures. One of the well characterized human epilepsy is temporal lobe epilepsy (TLE). TLE comprises of an initial

precipitating injury (IPI) caused due to head trauma, stroke, hypoxia, cardiovascular disease or infection followed by a latent period which ultimately leads to the development of chronic epilepsy (epileptogenesis) (Blair *et al*., 2009; Diamond and Blum, 2008; Hattiangady *et al*., 2011, Leppik e *et al*., 2006; Morillo, 2012). These pathological features of human TLE can be replicated in rodents by electrical stimulations (Reddy *et al*., 2010) or by chemoconvulsant drugs like kainic acid (Ben-Ari 1985, Dhanushkodi and McDonald 2011; Rao *et al*., 2006). Using animal models of TLE, significant insights have been obtained about the cellular and molecular events underlying the progression from IPI to TLE. However, as compared to young and immature subjects, studies investigating the effect of TLE in aged subjects are limited (Leppik *et al*., 2006). Few studies that investigated the effects of aging on seizure susceptibility revealed that minimal stimulation is sufficient to provoke SE resulting in massive neuronal loss, neuroinflammation and early development of TLE in aged rats (Blair *et al*., 2009; Hattiangady *et al*., 2011). Furthermore, the magnitude of co-morbidities associated with TLE such as cognitive impairment, depression, anxiety, problems with social life and motor function impairments are much higher in the aged population than in younger ones with TLE (Rowan 2005).

Anti-epileptic drugs (AED) are the most common means of treating TLE. However, nearly 30% of TLE patients do not respond to AED treatment. Moreover AED, rather than reducing the progression of the disease, is instead associated with unwanted side effects (Acharya *et al*., 2008; Gorter and Potschka 2012; Morillo 2012). In patients with retractable epilepsy, surgical resection of the temporal lobe is recommended. However, such procedures cannot be applied to all TLE patients and, particularly to aged individuals, due to surgery related complications and poor post- operative recovery. According to the World Health Organizations' recommendation for comprehensive epilepsy care, the therapeutic regime should comprise of psychosocial, cognitive, physical, educational and vocational aspects. This recommendation fits well with the concept of "activity dependent plasticity" that was proposed half a century ago by Donald Hebb (Hebb, 1947; 1949). One experimental paradigm that mimics Donald Hebb's proposal is an enriched environment (EE).

What is enriched environment?

The enriched environment which, in comparison to standard environment, provides enhanced possibilities for sensory, motor, cognitive and social stimulation (Rosenzweig *et al.,* 1962). Accumulating evidence suggest that environmental stimulation leads to significant neuronal plasticity (Kempermann *et al*., 1997; Kempermann and Gage, 1999). The enhanced neuronal plasticity following enriched housing condition was attributed to up regulation of various nerve growth factors. In 1997, Kempermann *et al.* demonstrated that housing rodents in enriched housing condition can enhance hippocampal neurogenesis, a form of neuronal plasticity in which new neurons are formed and integrated into already existing neuronal circuitry. We and other researchers have shown the positive impact of enriching the living environment for treating various brain injuries (Dhanushkodi *et al*., 2007; Dhanushkodi and Shetty 2008; Nithianantharajah and Hannan 2006). We have reported that housing subiculum lesioned rats in EE significantly prevents retrograde and anterograde hippocampal neuronal loss, enhances dendritic arborization and improves spatial learning and memory (Bindu *et al*., 2007; Bindu *et al*., 2005; Dhanushkodi *et al*., 2007). At synaptic level, Malik and Chattarji (2012) reported an enhanced CA1 long term potentiation in rats reared in EE which positively correlated with learning performance and CA1 dendritic spine density. In the context of EE and epilepsy, few studies that investigated the effect of EE in immature/young rodents with SE reported positive effect in terms of reduction in seizure intensity/frequency and cognitive performance (Auvergne *et al*., 2002; Faverjon *et al*., 2002; Koh *et al*., 2005; Kus *et al*., 2010; Rutten *et al*., 2002; Xie *et al*., 2012; Young *et al*., 1999). These studies suggest that enriched environment can assist in remodeling/correcting the neuronal circuitry in a neurodegenerative scenario and such phenomena would contribute to the functional recovery that was otherwise compromised in such disease conditions. Though these studies substantiate the beneficial effect of EE in various brain injury models, to our knowledge, there are not many studies which have investigated the effects of EE in aged epileptic subjects. In the subsequent section, we propose three hypotheses by which it can be addressed.

Proposed hypothesis

I. Exposure of aged rodents with status epilepticus to enriched environment prevents epileptogenesis and mitigates co-morbidities

Rodent model of TLE developed by using chemoconvulsant drugs like kainic acid has been an excellent tool for understanding the pathophysiology of TLE. This model mimics many clinical manifestations of human SE like hippocampal sclerosis, epileptogenesis and cognitive impairments. As hippocampus is the major foci of seizure in TLE, hippocampal dependent cognitive functions are compromised following SE. To address the hypothesis that exposure of aged subjects with SE to EE could prevent epileptogenesis and mitigate co-morbidities, aged rodents can be subjected to chemoconvulsant induced status epilepticus and then housed immediately in EE for a specific duration. Following enriched housing treatment, the seizure intensity, co-morbidities and hippocampal dependent cognitive functions can be assessed.

II. Exposure of chronically epileptic aged rodents to enriched environment mitigates co-morbidities associated with temporal lobe epilepsy

The KA model of TLE reproduces many aspects of the clinical condition of TLE including cognitive deficits, depression, anxiety and problems with social behavior. In order to address this hypothesis, aged rodents can be subjected to SE induction and housed in a standard rodent housing condition during the epileptogenic period (~ 2 months following SE) and later can be transferred to an enriched housing condition for a

specific period of time. Following that, the behavioral seizures, cognitive functions and co-morbidities like anxiety, depression and social behavior can be assessed.

III. Exposure of acute or chronically epileptic aged subjects to EE can restore endogenous anti-epileptic factors

To understand the molecular and cellular mechanisms underlying the anti-epileptic and cognition enhancing effects of EE, brain samples from acute and chronically epileptic rats can be assessed for hippocampal neuroprotection, neuroinflammation, neurogenesis, mossy fiber sprouting as well as the status of endogenous anti-epileptic factors.

Conclusion and Implications

The prevalence of seizure is higher in the elderly populations. In aged patients, co- morbidities are difficult to disassociate from normal age related problems like dementia, and intervention with AED often leads to several psychosomatic illnesses. Thus, exploring alternate non-invasive therapeutic strategies to treat elderly patients with TLE is warranted. The importance of the proposed hypotheses is that they help us understand the effects of EE at molecular-cellular-behavioral level. This would help basic researchers as well as clinicians who are trying to harness the therapeutic and regenerative potential of enriched environment/rehabilitation in preventing or treating epilepsy. If enriched environment is beneficial in aged subjects with TLE, it can be implemented at the clinical level as an adjuvant therapy in addition to AED treatment (probably at a lower dose) as it is a non-invasive procedure. However, an in-depth pre- clinical investigation is important to determine the specific time of intervention and positive effects and negative aspects of EE at molecular-cellular-behavioral level. The proposed hypotheses would address these questions.

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Conflict of Interest: Nil

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