1. Introduction

Modern concept of epilepsy originated in the middle of 19th century. According to which epilepsy was not a specific disease, or even a single syndrome, but rather a broad category of symptom complexes arising from any number of disordered brain functions that themselves may be secondary to a variety of pathologic processes. The terms convulsive disorder, seizure disorder, and cerebral seizures are used synonymously with epilepsy: They all refer to recurrent paroxysmal episodes of brain dysfunction manifested by stereotyped alterations in behavior. Therefore epilepsy can be defined as a heterogeneous biomedical disorder, with enormous variations in etiology and clinical features, resulting in irregular episodic bursts of electrical activity in certain neurons, which may spread to the entire brain (Bradford, 1995).

One of every ten people will have at least one epileptic seizure during a normal lifespan, and a third of these will develop epilepsy. It is one of the most common serious neurological disorders; affecting approximately 70 million people of all age worldwide (Ngugi et al., 2010). Around 80% of people with epilepsy belong to developing countries, where epilepsy remains a major public health problem, not only because of its health implications but also for its social, cultural, psychological and economic connotations (WHO, 2009; 2012). In India around 10 million people are suffering from epilepsy (Roy and Dhiman, 2013).

Epilepsy can be more complicated by neurobehavioral comorbidities, which include cognitive impairment, psychiatric disorders, and social problems. Most studies indicate that up to 50% of patients with epilepsy have psychiatric syndromes (Torta and Keller, 1999; Lambert and Robertson, 1999). The neurobehavioral comorbidities can be divided into two types: one is pathological (developed due to epilepsy itself) and 2) medical (developed due to antiepileptic drugs). Although such comorbidities are traditionally thought to arise predominantly from the effects of recurrent seizures, iatrogenic effects of medications, and adverse social reactions to epilepsy (eg, stigma), there is a growing body of evidence that other factors may also be involved. These influences include altered neurodevelopment of the brain, cognition, and behavior; exacerbation of the comorbidities due to decades of medically intractable epilepsy; and possible acceleration of common age-associated changes, leading to uncertain and understudied outcome in old age.
Cognitive comorbidity has been reported to have most debilitating effect on overall health care and quality of life in patients with epilepsy (Gaitatzis et al., 2004; LaFrance et al., 2008). Cognitive dysfunction in epileptic patients is as diverse as the epileptic condition itself. Literature evidences suggest strong correlation between cognitive dysfunction and variety of clinical epilepsy factors, including etiology, age of onset, seizure type and severity, duration, antiepileptic medications (Beghi et al., 2006). Nearly 30% of patients with epilepsy suffer from cognitive problems (Mojs et al., 2007).

Age related decline in learning and memory remains distinguishing feature of a variety of mammals, from humans to rodents and generally affects learning, working and reference spatial and long term memory (Frick et al., 2000). Impaired cognitive outcome is also generally associated with an early onset and a long duration of the disease and with poor seizure control (Elger et al., 2004). In similar way, age of onset of epilepsy is one of the major factors that have wide spread debilitating consequences on learning and memory deficit (Ingram, 1988; Flood and Morley, 1993; Moffat et al., 2001; Sanchetee and Sanchetee, 2007). Epilepsy with juvenile and geriatric onset of epilepsy is more vulnerable to behavioral comorbidities than the patients with adult onset (Haut et al., 2009; Desai, 2010).

Children with epilepsy are at increased risk of developing learning and memory deficit as compared to children either healthy or with other chronic illness (Williams, 2003; Rantanen et al., 2009; Vendrame et al., 2009). Approximately 30% of children with epilepsy have autism and/or intellectual or developmental disabilities (Tuchman et al., 2009) and 44% suffer from learning disability (Lee et al., 2006). In children it negatively affects their quality of life and represents a significant risk factor for academic under achievement, mental slowness, memory difficulties, attention deficits and social incompetency (Williams, 2003; van Rijckeversel, 2006; Fastenau et al., 2008). Similarly cognitive impairments with epilepsy also increase with advancing age (Haut et al., 2009). Generally the cognitive deficit left untreated due to under recognition or concerns over treatment worsening seizures (Kerr et al., 2009).

Almost every patient with epilepsy is dependent on antiepileptic drugs for their seizure control. However, only 70% of them get their seizure control with antiepileptic drug and rest show refractory epilepsy. Therefore management of
epilepsy appears ineffective with available antiepileptic drugs, resulting in poor seizure control (Elger, 2004), which poses a significant risk factor for progressive memory deficit in these patients.

Further adding to this woe, most of the available antiepileptic drugs, used to manage epilepsy may also cause memory deficit (Lagae, 2006, Vinayan, 2006; Marson et al., 2007; Eddy et al., 2011). Most commonly prescribed antiepileptic has been reported to be associated with cognitive decline in epileptic patients (Thompson et al., 1981; Aldenkamp et al., 1994; Meador et al., 1995). Phenytoin has long been suggested to produce worst cognitive performance as compared to other antiepileptic drugs (Meador et al., 1995). Another choice of drug for management of epilepsy, sodium valproate, has been reported to have lesser cognitive side effects as compared to other antiepileptic drugs (Trimble and Thompson, 1984; Marson et al., 2007; Sun et al., 2008). However some study suggests no clinical significant difference in phenytoin and sodium valproate (Meador et al., 1995) and some suggest higher risk of Parkinson related cognitive side effect of valproate (Ristić et al., 2006).

Owing to the risks of seizurogenic potential concerned with management of cognitive comorbidities with conventional memory enhancing drugs (Griffith et al., 2008), these patients often remain untreated. Therefore, clinical interventions to prevent these commodities in patients with epilepsy are still issues of substantial concern.

Epidemiology of the cognitive deficit is well studied in the epileptic populations but the research efforts to find the remedial measure for cognition deficit in epilepsy are negligible. Only few preclinical studies have been carried out but they are neither systematic not coordinated to conclude an appropriate management for this menace. Epilepsy Research Benchmarks 2007-2012, benchmark III also justifies the need of active research in this area.

Major lacuna in the experimental protocol of the studies (Mehla et al., 2010; Pahuja et al., 2012) reported till date for pharmacological interventions to treat the epileptic comorbidities that the pharmacological treatment strated along with induction of kindling. This does not ensure successful kindling which may obscure the true protective effect. This approach may be appropriate for secondary epilepsy (post traumatic brain injury). However, major chunk of the epileptic patients are of
primary epilepsy (idiopathic) and development of comorbidity occurs with controlled and uncontrolled chronic epilepsy. Therefore we propose that the treatment should be started after successful induction of kindling. Hence, the present study was envisaged to investigate pathobiology of cognitive deficit in post-kindled animals in search of possible safe target for the management of epilepsy and associated cognitive deficit.