CHAPTER I

INTRODUCTION

Management of epilepsy is a dynamic process, and the control of seizures may vary from time to time. There are more than 50 million epileptics worldwide. Some seizures can be controlled by the standard antiepileptic drugs (AEDs), including phenytoin, carbamazepine, barbiturates, benzodiazepines, valproate and ethosuximide. In addition, several newer agents; felbamate, gabapentin, lamotrigine, topiramate, and, most recently, levetiracetam, oxcarbazepine, and zonisamide, are also employed (Temkin, 2001; McAuley et al., 2002). However, seizures in many epileptic patients remain resistant to these antiepileptic drugs. Of these patients with refractory seizures, only a small percentage will become candidates for surgery. Another category of epileptic patients includes those whose seizures can be controlled, but on the experience of chronic toxicity associated with their medications (White, 1997). Therefore, gradual and orderly changes in antiepileptic drug therapy are often required, and there is still a need for new antiepileptic drugs with more selective action and fewer toxic effects.

The use of animal seizure models is essential in the discovery and development of new drugs for the treatment of epileptic seizures. The pilocarpine animal model of epilepsy is a common experimental tools in epilepsy research. This model has been proposed, on the basis of electroencephalographic (EEG), behavioral, and morphologic features, as an animal model resembling some aspects of human temporal lobe epilepsy (TLE) (Turski et al., 1983; Cavalheiro et al., 1991; Mello et al., 1993). After pilocarpine injection, the animal became hypoactive; followed by generalized convulsions and limbic status epilepticus (SE) that caused neuronal loss and mossy fiber sprouting in hippocampus and subsequently spontaneous recurrent seizures (SRS) (Turski et al., 1983; Cavalheiro et al., 1991). Many microdialysis studies demonstrated significant alterations of glutamate and γ-aminobutyric acid (GABA) concentrations in pilocarpine-induced seizure (Walton et al., 1990; Cavalheiro et al.,

1994). In addition, Smolders and co-workers (1997) demonstrated that changes in extracellular hippocampal amino acids levels (glutamate, aspartate and GABA) are not involved in seizure onset, but might play a role in seizure maintenance and spread in the pilocarpine animal model of epilepsy. The fact that pilocarpine induced status epileticus is followed by changes in the level of lipid peroxidation in the hippocampus, suggesting that reactive oxygen species (ROS) could be involved in the neuronal damage induced by pilocarpine (Dal-Pizzol et al., 2000).

N-(2-propylpentanoyl) urea (VPU) is an analog of valproic acid (VPA) which is an effective anticonvulsant agent for the management of most forms of epilepsy including pilocarpine-induced seizure model (Turski et al., 1983; Johannessen, 2000). VPU has demonstrated a higher protection than VPA in both the maximal electroshock seizure (MES) and the pentylenetetrazole (PTZ) tests by exhibiting a median effective dose (ED_{50}) of 66 and 57 mg/kg, respectively. Furthermore, VPU produced less neurological side effects and higher protective index (9.5) than VPA (1.1) (Tantisira et al., 1997). In microdialysis studies, VPU decreased glutamate, aspartate, GABA and glycine in anesthetized rat (Sooksawate, 1995). Additionally, it depressed spontaneous firing of both neurons of cerebral cortex and cerebellum recorded by microiontophoretic technique in anesthetized rats (Khongsombat, 1997).

However, no data of VPU in pilocarpine-induced seizure model is available. Thus, we considered it is interesting to study the effects and underlying mechanisms of VPU in pilocarpine-induced seizure model. We studied an anticonvulsant activity of VPU against pilocarpine-induced seizure. Furthermore, effects of VPU on neurochemical changes (excitatory and inhibitory amino acid neurotransmitters in the hippocampus), neuronal cell loss in hippocampus (CA1 and CA3 regions), lipid peroxidation and neuronal mitochondrial function were also investigated.

CHAPTER II

REVIEW LITERATURES

Epilepsy

Epilepsy is a common neurological disorder which is characterized by a tendency to recurrent seizures (McNamara, 1999; Thom, 2004).

A seizure is the manifestation of an abnormal and excessive synchronized discharge of a set of neurons in the brain. The clinical features are sudden and transient and include a wide variety of motor, psychic and sensory phenomena, with or without alteration in consciousness and awareness (Shorvon, 2000; Bittigau et al., 2002).

Status epilepticus (SE) is defined as a condition in which epileptic seizures continue, or are repeated without regaining consciousness, for a period of 30 min or more (Shorvon, 2000).

There are more than 50 million epileptics worldwide. Epileptic seizures affect all age groups and can be the result of an acute or chronic cerebral illness (Thom, 2004). The incidence of epilepsy is slightly higher in men than in women (Annegers, 1993) and appears to be higher in African-Americans than in Caucasians (Haerer, Anderson, and Schoenberg, 1986). With exclusion of all other known factors, age alone constitutes a risk for epilepsy with a magnitude of 1.3 for every decade of life over the age of 30 (Ng et al., 1993). Interestingly, this age dependence of the incidence of epilepsy has shifted over recent years. Whereas the majority of epilepsies were once manifested in childhood and adolescence, today, the incidence is higher in persons over the age of 65 than during the first 2 decades of life. Epilepsy is the third most frequent neurological disorder encountered in the elderly after cerebrovascular disease and dementia (Kramer, 2001). In addition, population-based epidemiological studies demonstrate that SE, a severe form of seizures, has a much greater incidence than previously reported and like epilepsy, also manifests the highest incidence in childhood and in the elderly (DeLorenzo et al., 1996).