Chapter I

Introduction

The epilepsies are one of the most common neurological disorders. If one estimates that 1% of the world's population has epilepsy, then about 50 million persons worldwide suffer from this disorder. Globally, the prevalence of this disorder was nearly 0.5-1.0 % of every age. About 75 % of patients with epilepsy have the first seizures in childhood and begin before the age of 18 years. Only 80% of the patients have succeeded in controlling the symptom while 20 % failed to do so (Penry, 1988; Porter, 1993).

It is estimated that the incidence and prevalence of epilepsy in Thailand were similar to those reported in other countries, though no precise epidemiologic studies have been ever taken. Together with the fact that Thai population has many predisposing factors such as high rate of accident, viral encephalitis, parasite, pesticide and alcohol problem, epileptics impose a major public health problem to the country (นิพนธ์ พวงวรินทร์, 2533).

The major therapy for seizures is drug therapy. The ideal antiepileptic drug would obviously suppress all seizures without causing any unwanted effects (Rall and Schleifer, 1990). Multiple classes of antiepileptic drug have been used because of variable selectivity against the epilepsies (Penry, 1988). Though many patients have benefited from the progress of antiepileptic therapy, some patients continue to suffer (Bialer et al., 1994). There are many unsatisfactory aspects of the drug treatment of

epilepsy, in particular the widespread use of multiple drugs which result in long term toxic consequences. A large number of drugs known to suppress seizure cause rashes, stomach upsets, and at higher doses, sedation which is a particular problem with the older drugs chemically related to barbiturates (Burnham, 1989). In addition, inappropriate use of antiepileptic drugs could exert a negative effect on a child's cognitive and social development (Penry, 1988).

Most patients receiving polytherapy continue to have seizures along with other problems such as chronic toxicity, drug interactions, increased risk of serious idiosyncratic adverse reactions and a significant increase in the cost of medications compared with monotherapy (Wilder and Rangel, 1988). Thus the monotherapy approach is a preferred therapeutic regimen over polytherapy.

Valproic acid (VPA) is one of antiepileptic drugs of choice that has been widely used in the treatment of several types of seizures (Alldredge, 1992). It is effective in controlling generalized and partial seizures, particularly as monotherapy. However, it has two major side-effects namely teratogenicity and hepatotoxicity (Porter, 1993). It is more expensive and has a short half-life (6-15 hours) (Penry and Dean, 1993). Valproate is less potent than the other established antiepileptic drugs: phenobarbital, phenytoin and carbamazepine (Bialer et al., 1994). Thus, there is a need for new antiepileptic drugs which possess a higher potency but lower toxicity.

(N-hydroxymethyl)-2-propylpentamide (HMV) is a valproate derivative consisting of VPA and hydroxymethylamide. It was synthesized by Assistant Professor Dr. Chamnan Patarapanich in a search for a valproate analogue which is more effective but less toxic than its parent compound. In preliminary screening, HMV has exerted a certain extent of anticonvulsant activity (Unpublished observation).

The present studies, therefore, aim to evaluate anticonvulsant activity of HMV in several animal models of epilepsy as well as its adverse effects and acute toxicity. Furthermore a possible effect of HMV on brain GABA, a neurotransmitter generally known to play an important role in pathogenesis of epilepsy, is also investigated in cerebral cortex of the rats.