Chapter 1

INTRODUCTION
## CONTENTS

1. Present Status of Antiepileptic Drug Therapy is Grossly Inadequate  
   Page 3

2. Cognitive Function Disturbances  
   Page 4

3. Concept of an Inverse Relationship between Seizure Control and Cognitive Function: Is it unavoidable?  
   Page 4

4. Epilepsy, Cognitive Functions and Histamine  
   Page 5

5. Therapeutic Potential of H3-receptor Ligands  
   Page 6

6. Intracellular Calcium  
   Page 7

7. AED Therapy: Rational Polypharmacy and a Mechanism Based Approach  
   Page 8
1. Present Status of Antiepileptic Drug Therapy is Grossly Inadequate

Epilepsy is one of the most common neurological disorders with an estimated prevalence of 50 million people worldwide (Perucca, 1996). The incidence is much higher in developing countries (0.25-1.5%) (Delgado-Escueta et al., 1986; Shorvon and Farmer, 1988) than in developed countries (0.031-0.057%) (Dichter and Buchhalter, 1997; Vohora, 1997). Upto the late 80s, only a handful of antiepileptic drugs (AEDs) were available. The last two decades, however, saw the introduction of several novel AEDs already licensed in various parts of the world or expected to be licensed in the near future (Perucca, 1996; Sharma et al., 1996; Blum, 1998; Dichter, 1998). Inspite of these advances, the treatment for epilepsy is symptomatic and far from adequate even today (Shin and McNamara, 1994; Beghi and Perucca, 1995). Available drugs reduce seizure frequency in the majority of the patients, but only 40% are free from seizures despite optimal treatment. Neither an effective prophylaxis nor a cure of this disorder is available except a neurosurgical resection of epileptic tissue in selected instances (McNamara, 1994). Besides, the currently available AED therapy is associated with a variety of adverse effects and is not ideal in terms of adverse drug interactions with other AEDs, psychotropic drugs and other drugs (Mattson, 1995; Perucca, 1996). Obviously, there is an urgent need to identify the problems associated with drug therapy in epilepsy. Since antiepileptic treatment may last a lifetime in many patients, the aim of the treatment is therefore to attain the best compromise between the desire to maximize seizure control and the need to keep the side effects within acceptable limits. It is hoped that understanding the cellular and molecular mechanisms of epilepsy as well as
the development of novel AEDs will lead to improved therapies and new insights into brain structure and function.

2. **Cognitive Function Disturbances**

A significant proportion of epileptic patients experience memory disturbances. This is well documented and several reports are available on the subject (Dodrill 1986; Halgren et al., 1991; Smith, 1991; Thompson, 1991, 1992; Vermeulen and Aldencamp, 1995). The origin of such cognitive function disturbances has been attributed to several factors, both biological and psychosocial. These stem from: a) the disease itself (Halgren et al., 1991) and b) AED therapy (Vermeulen and Aldencamp, 1995). Thus, while the underlying brain pathology, type, frequency and severity of seizures and psychosocial factors play an important role, paradoxically the therapy used also adds to the problem. It is thus important to know to what extent the memory disturbances are caused by the medication and whether all AEDs influence memory in the same negative way. Such investigations are difficult to carry out clinically as many patients are on polymedication. Thus, it would be of interest to study the effect of known seizure inducing agents as well as AEDs on experimental models of learning and memory.

3. **Concept of an Inverse Relationship between Seizure Control and Cognitive Function: Is it unavoidable?**

A close look at the scientific data available on the subject suggests an inverse relationship between cellular mechanisms underlying seizure control and
cognitive function. Both epilepsy and cognitive function have been linked to abnormalities in the excitatory amino acid (EAA) neurotransmission, long-term potentiation (LTP) and GABAergic inhibition in an opposite manner (Figures 2.1 and 2.2, Table 2.15, Chapter 2). Further, epilepsy and memory are reported to share the same anatomical loci in the brain in such a way that the regions of brain, considered important for memory, may provoke a seizure (Halgren et al., 1991; Thompson, 1991). Such biological/pharmacological antagonism (e.g. cognitive deficits by AEDs) has been responsible for compromises in the therapeutic approach towards drug therapy and the management of epilepsy for decades. A concerted effort is needed for a breakthrough in this unfortunate situation. Two approaches can be explored: i) Histamine and drugs enhancing histaminergic neurotransmission appear to have a beneficial role in both seizures and learning/memory processes. Drugs targeting histamine receptor ligands, should therefore, be a rational approach with great promise. ii) Investigating the practice of rational polypharmacy in epilepsy management for reducing drug doses, toxicity and adverse effects.

4. Epilepsy, Cognitive Functions and Histamine

Epilepsy research has largely been targeting GABAergic and glutamatergic neurotransmission mechanisms. It is felt that the histaminergic neuronal systems have not received the requisite attention towards understanding the basic mechanisms involved in the disease and also in the development of AEDs. There is now considerable scientific evidence that the central histaminergic neuronal system plays an important role in the inhibition of seizure activity. The first early
evidence for the involvement of histamine came from animal studies in which drugs that deplete brain histamine were found to potentiate convulsions and vice versa (Tuomisto and Tacke, 1986; Yokoyama et al., 1992). Moreover, the direct histamine $H_1$-receptor activation or modulation of central histamine levels by l-histidine loading and the inhibition of histamine synthesis or its metabolism in rodents indicate histamine to be an endogenous anticonvulsant (Yokoyama et al., 1992, 1994a; Leurs et al., 1998). In addition to the role of histamine on seizures, experimental and clinical evidence exists for its role in learning and memory. While intracerebroventricular (icv) administration of histamine and $H_1$-receptor agonists are reported to facilitate various memory tasks (De Almeida and Izquierdo, 1986, 1988; Kamei and Tasaka, 1992, 1993), histamine depletors and $H_1$-blockers show impairment (Kamei and Tasaka, 1991; Kamei et al., 1993). Further, histamine levels were found to be significantly lower in the brains of patients with Alzheimer’s disease (Marurkiewicz-Kwilecki and Noswah, 1989) and a possible therapeutic use of histamine receptor ligands was suggested in this disease (Onodera et al., 1994). These facts point to the relevance of more scientific investigations on such lines towards the understanding and management of epilepsy without compromising on cognitive ability.

5. Therapeutic Potential of $H_3$-receptor Ligands

Presynaptic control via $H_3$-receptors (autoreceptors) is an important mechanism of histamine mediated neurotransmission (Arrang et al., 1983). Antagonists of $H_3$-receptors have been a subject of considerable research interest since their discovery by Arrang and co-workers (1987). These agents appear to be useful
investigative tools in behavioral studies according a certain degree of protection in neurodegenerative, cognitive and convulsive disorders (Schwartz et al., 1991; Wada et al., 1991; Mochizuki et al., 1996). It would, therefore, be of interest to explore the therapeutic use of H₃-receptor ligands in epilepsy and cognitive function. Some reports of the protective action of thioperamide, an H₃-receptor antagonist, are available against maximal electroshock (MES)-induced seizures in mice (Yokoyama et al., 1993a). However, these effects appear partial to clonic convulsions with only a marginal effect on tonic convulsions. Thus, it would be worthwhile to explore the use of thioperamide in petitmal (clonic) epilepsy by studying its effect on pentylenetetrazole (PTZ)-induced convulsions, a model relatively specific for clonic convulsions in mice. Methionine-sulfoximine (MSO), a convulsant, is known to increase the activity of histamine-N-methyl-transferase (Schatz and Sellinger, 1975), the enzyme primarily responsible for the catabolism of histamine (Schayer and Railly, 1970). It would, thus, be of interest to study the effect of thioperamide against MSO-induced convulsions.

6. **Intracellular Calcium**

Calcium ions (Ca²⁺) are known to play a critical role in neurotransmitter release and signal transduction (Augustine et al., 1985, 1991), physiopathology of the nervous system (DeCoster, 1995), pathological events in various central nervous system (CNS) disorders e.g. epilepsy, Alzheimer's and Parkinson's disease (Jimenez-Jimenez et al., 1996), action of conventional as well as newer AEDs (Sohn and Ferrendelli, 1973; DeLorenzo, 1988; Stefani et al., 1997) and in the
regulation of cognitive deficits (Chen, 1998; Norris et al., 1998). Large differences in the intra- and extracellular Ca\(^{2+}\) ion concentrations highlight the vital role of the mechanisms controlling their influx and efflux (DeCoster, 1995). The loss of such regulatory activity is known to result in abnormally high intracellular calcium levels leading to a cascade of events with cytotoxicity and neuronal death (Jimenez-Jimenez et al., 1996). Their role in signal transduction at H\(_2\) receptors has not been elucidated. Several AEDs have been shown to regulate the entry of Ca\(^{2+}\) into cells through both voltage and transmitter regulated Ca\(^{2+}\) channels. Studies have demonstrated either a block of Ca\(^{2+}\) levels or a reduction in intracellular Ca\(^{2+}\) levels by both conventional (phenytoin, carbamazepine, sodium valproate, benzodiazepines, phenobarbitone) and some of the newer (felbamate, lamotrigine) drugs (Sohn and Ferrendelli, 1973; DeLorenzo, 1988; Stefani et al., 1997). Recently, it was suggested that the antiepileptic activity of gabapentin (GBP) is not due to a direct effect on receptors for inhibitory or excitatory amino-acids (Kelly, 1998). Reduction in synaptic Ca\(^{2+}\) entry has been speculated as a possible mechanism (McLean, 1999).

7. **AED Therapy: Rational Polypharmacy and a Mechanism Based Approach**

Contemporary antiepileptic therapy is neither universally effective nor invariably safe. Advances in the knowledge of mechanisms of epilepsies would allow for more rational therapeutic approaches to this difficult neurological disorder (Shin and McNamara, 1994). Indeed, the present era of AED development is driven largely by a greater understanding of the molecular mechanisms underlying
seizure disorders (Rogawski, 1998; White et al., 1998). Current practice suggests that combining drugs with different mechanisms is likely to optimise the therapeutic response.

AED monotherapy, currently the preferred regimen, may not be effective in many refractory patients of epilepsy. Addition of a second drug may prove beneficial in such cases (Gordon et al., 1993). A combination with additive or synergistic potential is obviously desirable (Bourgeois, 1986). It will hopefully help in achieving not only better seizure control but also in minimizing the risk of associated drug toxicity by reducing the doses of AEDs. Combination of AEDs with H3 receptor antagonists and known nootropic agents appear to be promising directions for research in this area for maximal seizure control with no (minimal) cognitive deficits. As epilepsy is a chronic disease requiring long-term therapy, it is absolutely essential that such combinations should incorporate drugs with minimal chances of iatrogenic effects. Natural products (e.g. medicinal plants), which have been in use since generations in traditional systems of medicine, may provide many such relatively safe drugs.

Cholinergic mechanisms, though extensively investigated for a role in cognitive functions, do not provide a complete account for such deficits in ageing or Alzheimer's disease. Such deficits occur within the context of alterations of other neurotransmitter systems (Decker and McGaugh, 1991; Morisset et al., 1996). A close relationship exists between the cholinergic and the histaminergic systems in learning and memory (Smith et al., 1994; Onodera et al., 1998). Recently, tacrine was reported to inhibit histamine-N-methyl-transferase activity and to augment cerebral histamine levels (Nishibori et al., 1991). Thus, the association of tacrine and an H3-receptor antagonist might represent a novel therapeutic approach in this area.