Chapter I

Introduction

Epilepsy

Epilepsy, from the Greek *epilepsia* (a taking hold of, or seizure) is a chronic disorder characterized by a spontaneous tendency for recurrent seizure. Seizures are the clinical manifestation of abnormally hyperexcitable cortical neurons. Whereas all patients with epilepsy have seizures, many more patients have a single seizure during life and are not considered to have epilepsy. (Foldvary and Wyllie, 1999; Greene and Harris, 2000;Trescher and Lesser, 2000;Victor and Ropper, 2001)

The characteristic event in epilepsy is the seizure, when is associated with the episode high-frequency discharge of impulses by a group of neurons in the brain. What starts as a local abnormal discharge may then spread to other areas of the brain. The site of the primary discharge and the extent of its spread determines the symptoms that are produced, which range from a brief lapse of attention to a full-brown convulsive fit lasting for several minutes. The particular symptoms produced depend on the function of the region of the brain that is affected. The involvement of the motor cortex causes convulsions; involvement of the reticular formation in the upper brainstem leads to loss of consciousness. (Rang, Dale,and Ritter, 1999;Lott and McAuley, 2000; Victor and Ropper, 2001)

Approximately 1 % of the world's population has epilepsy, the second most common neurology disorder after stroke. Although standard therapy permits control of seizures in 80% of these patients millions (500,000 people in the U.S.A alone) have uncontrolled epilepsy (Porter and Meldrum, 2001). Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. (McNamara, 2001)

1. Etiology

Epilepsy can arise from a variety of conditions and pathophysiologic mechanism. About 70 % of adults and 40% of children with new-onset epilepsy have partial (focal) seizures. In most of these, it is not possible to identify a specific cause, although the focal nature of the seizures generally implies a cerebral injury or lesion (so-called cryptogenic epilepsy). The most common specific lesions are hippocampal sclerosis, gangliogliomas and glial tumor, cavernous malformations, neuronal migational defects (cortical dysplasia) and hematomas, encephalitis, cerebral trauma and hemorrhage. Not all patients with cerebral pathology have epilepsy; have a particular lesion or injury causes a region of brain to become epileptogenic is still poorly understood. (Pedley, 2002)

Although specific mendelian (e.g., tuberous sclerosis, hyperglycenemia, Laford's disease), chromosomal (e.g., Down syndrome), and mitochondrial (e.g., MELAS) genetic disease account for only about 1% of epilepsy case, heritable factors are important in a much higher percentage, especially in children. Forms of epilepsy that are demonstrably more heritable than others (e.g., childhood absence epilepsy, juvenile myoclonic epilepsy) are increasingly refer to as idiopathic or primary epilepsies. Common features include a variable family history, generalized spike-wave abnormality on electroencephalogram (EEG), and onset in childhood or adolescence.

Family history, cerebral injury, and neurological disease are all risk factors for epilepsy, and the magnitude of the increased risk relative to the population at large can be specified for a number of different conditions that predispose to seizures. In many patients, several factors coexist, and the development of epilepsy reflects the interaction of acquired brain pathology and genetic predisposition. (Avoli, 1997; Pedley, 2002)

Genetics in epilepsies

It has long been known that epilepsy is a major genetic component to febrile seizure. A family history of febrile seizures consistently emerges as the major risk factor for a first febrile seizure and twin (Berg and Shinna, 1995). Although autosomal dominant and recessive models of heritance have been proposed, most evidence favors a complex mode of inheritance, that is polygenic or multiplefactorial (Buchhalter, 1993; Berkovic and Scheffer, 1998).

2. Epileptogenesis

The morphological abnormalities associated with epilepsy do not explain how seizures develop or propagate. The hypothesis that single or small groups of epileptic neurons into seizure activity is being challenged by concepts involving the plasticity of normal neurons in adapting to changes in their environment. (Trescher and Lesser, 2000)

2.1 Neuronal Plasticity

At the extremes, neuronal plasticity may be responsible for the neuronal hyperexcitability and hypersynchrony that are primary features of epileptiform activity (Schwartzkroin, 1993). Neuronal plasticity has been shown in mesial temporal sclerosis and in experimental models of hippocampal injury after kindling. When neurons are lost, abnormal sprouting of fiber terminals with synaptic reorganization occurs. The pattern of reorganization is not random but occurs in a way that may support epileptic activity of the abnormal hippocampus. Although synaptic reorganization has been most extensively studied in the hippocampus, it also may play a role in epileptic activity in the cortex.

Investigations of the mechanism of epileptic activity are beginning to address the interplay of the intrinsic electrical properties of the neuronal against a background of the activity of entire cell populations. The electrical behavior of the cells, which is central to the normal as well as the abnormal activity of the neurons

depends on ion conductance, primarily of sodium, calcium, potassium, and chloride. The ion conductance depends on the intra-and extra cellular concentrations of these ions as well as the ionic flux across the cell membrane. Ion flux across the cell membrane is controlled by a combination of energy-dependent pumps, voltage-gated channels, and neurotransmitter controlled channels. (Trescher and Lesser, 2000)

2.2 Neurotransmitter Systems

Neuronal interactions depend to a large degree on neurotransmitter systems; γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. GABA subclass A ($GABA_A$) receptors mediate flux of chloride across the membrane, which typically produces a membrane hyperpolarization and inhibition of neuronal activity. $GABA_A$ receptor blockade produces epileptic activity in experimental models, but the role of GABA inhibition in chronic epilepsy is less clear. Benzodiazepines bind to a modulatory site of $GABA_A$ receptor complex to increase the binding efficacy of the receptor for GABA. The $GABA_A$ subclass B ($GABA_B$) receptor also produces hyperpolarization but through a different mechanism, specifically modulation of potassium channels via a guanosine triphosphate-binding protein-mediated intracellular messenger system. Many of the cortical GABAergic neurons, which are interneuron, may have an important role in controlling epileptic activation of neurons. (Barnard et al, 1998; Trescher and Lesser, 2000; Treiman, 2001)

Glutamate is the major excitatory neurotransmitter in the CNS. It activates several receptor subtypes. The N-methyl-D-aspartate (NMDA) receptor is an ionophore complex that mediates calcium flux. Antagonist of the NMDA receptor have antiepileptic activity; but several in vitro and in vivo studies suggest that the NMDA receptor has a greater role in epileptogenesis than in maintaining already developed seizures. The non-NMDA ionotropic receptors primarily mediate fast synaptic transmission through sodium and potassium flux. The role of these non-NMDA receptors in epilepsy is less clear but is under active investigation. Other neurotransmitter systems play a modulating role in epileptogenesis. In addition to abnormalities of receptors themselves, dysfunction of neurotransmitter transport,

particularly glutamate and GABA, may contribute to seizures. (Meldrum, 1997; Trescher and Lesser, 2000)

2.3 Ion channels

The identification of an abnormality in a potassium channel as an underlying defect in benign familial convulsions highlights the importance of ion channels in epilepsy. Many of the anticonvulsants influence the voltage-dependent sodium channel, and abnormalities in this channel may underlie some heritable forms of epilepsy (Meldrum, 1997). Similarly, calcium channels may influence epilepsy through their role in modulating neurotransmitter release. (Trescher and Lesser, 2000)

2.4 Ion exchangers

Na^+/ H^+ and H^+/ HCO_3^- exchangers have been implicated in experimental absence seizure model. (Meldrum, 1997) The antiepileptic effect of carbonic anhydrase inhibitors may be explained in part by the block of the depolarizing effects of intracellular HCO_3^- with intense GABA receptor activation.

2.5 Regional Differences

Regional differences exits for seizures susceptibility and propagation. Even specific neuronal populations within regions, such as pyramidal neurons in the hippocampus or layer V cortical neurons, have a greater propensity to spontaneous bursting, possibly skin to interictal epileptiform activity (Schwartzkroin, 1993). Other regions, such as the entorhinal cortex or the area tempestas in the piriform cortex, may actually be bigger zones for seizure activity. In addition to these seizure-prone regions, other regions, such as the granule cell layer of the dentate gyrus or substantia nigra pars reticulata, serve as gating regions that may control seizure spread. (Trescher and Lesser, 2000)

3. Classification of seizures

Seizures are classified by their clinical manifestation (semiology) supplemented by EEG data. There are many different kinds of seizure, each with characteristic behavioral changes and electrophysiological alterations that usually can be detected by EEG recordings. The particular manifestations of any single depend on several factors: (1) whether most or only a part of the cerebral cortex is involved of the beginning; (2) the functions of the cortical areas where the seizure originates; and (3) the subsequent pattern of spread within the brain. The International Classification reflects these considerations in two important ways. First, it divides into two fundamental types: those with onset limited to part of one cerebral hemisphere (partial or focal seizures) and those that involved the cerebral cortex diffusely from the beginning (generalized seizures). Second, the International Classification recognizes that seizures are dynamic and evolving and that patients show variations in seizure pattern depending on the extent and manner of spread of the electrical discharge. Thus, simple partial seizures can evolve into complex partial seizures, and either simple or complex partial seizures can evolve into secondarily generalized tonic-clonic convulsions. (Pedley, 2002)

Table1. Classification of epilepsy (from Dreifuss, 1997)

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I. Partial seizure (seizure beginning locally)

    A. Simple partial seizures (seizures beginning locally)

        1. With motor symptoms

        2. With somatosensory or special sensory symptoms

        3. With autonomic symptoms

        4. With psychic symptoms

    B. Complex partial seizures (consciousness impaired)

        1. Simple partial onset followed by impaired conscious

            a. With simple partial features as in A.1-4

            b. Without automatisms

        2. With impairment of consciousness at onset

            a. With no other features

            b. With partial feature as in A. 1-4

            c. With automatisms

    C. Partial seizures evolving to secondarily generalized seizures

II. Generalized seizure

    A. Absence seizure

        1. Absence seizure

        2. Atypical absence

    B. Myoclonic seizures

    C. Clonic seizures

    D. Tonic seizures

    E. Tonic clonic seizures

    F. Atonic seizures

III. Unclassified epileptic seizures

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Modified from Commission on Classification of International League Against Epilepsy

4. Amino acid neurotransmitters in epilepsy

Effects on synaptic transmission have been sough for many antiseizure drugs. Enhancement of GABA-mediated inhibition can be produced in many different ways, involving either direct action on the GABA receptor-chloride channel complex (as with benzodiazepines, barbiturates, and possibly topiramate) or actions on the reuptake or metabolism of GABA (as with gabapentin, tiagabine, and vigabatrin). This mechanism provides protection against generalized and focal seizures.

Reduction of excitatory glutamatergic neurotransmission is potentially important; AMPA receptor blockade probably contribute to the effect of phenobarbital and topiramate, and NMDA receptor blockade probably contributes to the effect of racemide, an investigational drug. (Rang, Dale, Ritter, and Gardner, 2001)

4.1 Inhibitory amino acid neurotransmitters

GABA is the main inhibitory transmitter in the brain. In the spinal cord and brainstem, glycine is also important.

4.1.1 γ-Aminobutyric acid

GABA occurs in brain tissue, but not in other mammalian tissues, except in trace amounts. In the brain it is particularly abundant (about 10 μmol/g tissue) in the nigrostriatal system, but occurs at lower concentrations (2-5 μmol/g) throughout the gray matter.

GABA is formed from glutamate by the action of glutamic acid decarboxylase (GAD), an enzyme found only in GABA-synthesizing neurons in the brain. Immunohistochemical labeling of GAD is used to map the GABA pathways in the brain. GABA is destroyed by a transamination reaction, in which the amino group is transferd to α-oxa-oglutaric acid (to yield glutamate), with the production of succinic semialdehyde, and then succinic acid. This reaction is catalyzed by GABA-transaminase (GABA-T), which is inhibited by vigabatrin, a compound used to treat

epilepsy. GABA-ergic neurons have an active GABA uptake system, and it is this, rather than GABA-T, which removes the GABA after it has been released. .

GABA function as an inhibitory transmitter in many different CNS pathways. It is released from short interneurons, the long GABA-ergic tracts being those running to the cerebellum and striatum. The widespread distribution of GABA, and the fact that virtually all neurons are sensitive to its inhibitory effect, suggest that its function is ubiquitous in brain. It has estimated that GABA serves as a transmitter at about 30% of all the synapses in the CNS.

In common with glutamate, and several other CNS transmitters, GABA acts on two distinct types of receptor, one (the $GABA_A$ receptor) being a ligand-gated channel, the other ($GABA_B$) being a G-protein-coupled receptor. (Holmes, 1997; Olsen and DeLorey, 1999; Olsen, DeLorey, Gordey and Heekang, 1999; Treiman, 2001; Rang, Dale, Ritter, and Gardner, 2001)

$GABA_A$ receptors

The $GABA_A$ receptors are part of a larger GABA-drug receptor Cl^- ion channel macromolecular complex. The complex includes five major binding domains (fig.1). These include binding sites localized in or near the Cl^- channel for GABA, benzodiazepines, barbiturates and picrotoxin as well as binding sites for the anesthetic steroids. These binding domains modulate receptor response to GABA stimulation. In addition, other drugs, including volatile anesthetics, ethanol and penicillin, have been reported to have an effect on this receptor. An integral part of this complex is the Cl^- channel. The GABA-binding site is directly responsible for opening the Cl^- channel. A variety of agonists bind to this site and elicit GABA-like responses. One of the most useful agonist is the compound muscimol, a naturally occurring GABA analogue isolated from the psychoactive mushroom *Amanita muscaria*. It is a potent and specific agonist at $GABA_A$ receptors and has been a valuable tool for pharmacological and radioligand-binding studies. The classical $GABA_A$ receptors antagonist is the convulsing bicuculline, which reduces current by decreasing the opening frequency and mean open time of the channel. It is likely that bicuculline produces its antagonistic effects on $GABA_A$

receptors currents by competing with GABA for binding to one or both sites on the GABA$_A$ receptors. (Holmes, 1997; Olsen and DeLorey, 1999 Olsen, DeLorey, Gordey and Heekang, 1999; Treiman, 2001; Rang, Dale, Ritter, and Gardner, 2001)
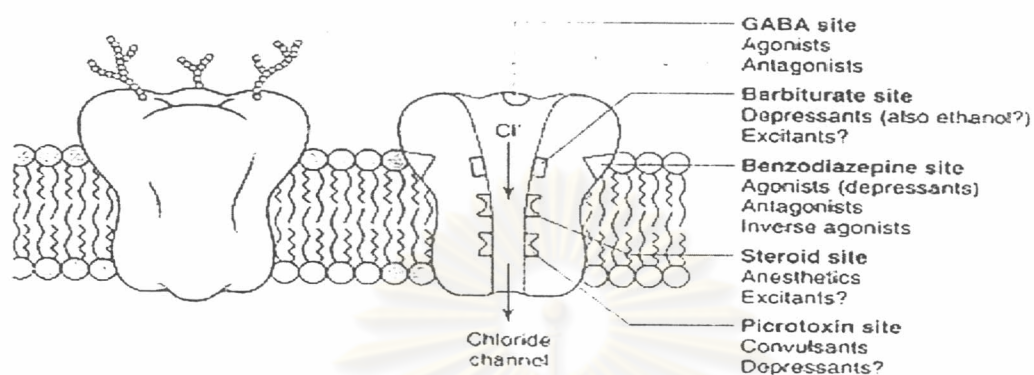

Figure 1 Structural model of the GABA$_A$ receptor

Benzodiazepine receptor-chloride ionophor complex. The cut-away view demonstrates targets for a variety of compounds that influence the receptor complex. Nonspecific drug receptor location is implied. (From Olsen and DeLorey, 1999)

Benzodiazepines, which have powerful sedative and anxiolytic effects, selectively potentiate the effects of GABA$_A$ receptors. They bind with high affinity to an accessory site (the "benzodiazepine receptor") on the GABA$_A$ receptors in such a way that the binding of GABA is facilitated and its agonist effect is enhanced. Studies on recombinant GABA$_A$ receptors have shown that a small region of the γ-subunit confers benzodiazepine sensitivity, and mutations affecting this region alter the level of constitutive activity at this site, and its sensitivity to benzodiazepine. Sedative benzodiazepines, such as diazepam, are agonists (enhancing the action of GABA), whereas convulsing analogs, such as flumazenil, are antagonists.

Modulators that also enhance the action of GABA, but with sites of action that are less well defined than that of benzodiazepines (shown as "channel modulators") include other CNS depressant such as barbiturates and neurosteroids. Neurosteroids

are compounds that are related to steroid hormones but do not act on conventional intracellular steroid receptors. Interestingly, they include metabolites of progesterone and androgens which are formed in the nervous system, and have a physiological role. Synthetic neurosteroids include alphaxolone, developed as an anesthetic agent.

Picrotoxin is a convulsing that acts by blocking the chloride channel associated with the $GABA_A$ receptors, thus blocking the postsynaptic inhibitory effect of GABA. It has no therapeutic uses. (Rang, Dale, Ritter, and Gardner, 2001)

$GABA_B$ receptors

Less is known about the $GABA_B$ receptors, primarily due to the limited number of pharmacological agents selective for this site. Originally, $GABA_B$ receptors were identified by their insensitivity to the $GABA_A$-specific agonist. The GABA analog(-)baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid) was found to be a potent and selective $GABA_B$ agonist.

$GABA_B$ receptors are coupled indirectly to K^+ channels. When activated, these receptors can decrease Ca^{2+} conductance and inhibit cAMP production via intracellular mechanisms mediated by G proteins. $GABA_B$ receptors can mediate both postsynaptic and presynaptic inhibition. Presynaptic inhibition may occur as a result of $GABA_B$ receptors on nerve terminals causing a decrease in the influx of Ca^{2+}, thereby reducing the release of neurotransmitters. The cloning of the $GABA_B$ receptors an its structural similarity to the metabotropic glutamate receptors should allow rapid progress in the pharmacological characterization of receptor subtypes and the development of new drugs of improved selectivity. Pharmacological responses to GABA that are insensitive to both bicuculline and baclofen have been termed $GABA_C$ receptors. Some, but not all, of these responses can be explained by a structural analog of $GABA_A$ receptors, the ρ subunit. (Olsen and DeLorey, 1999)

4.1.2 Glycine

Glycine is present in particularly high concentration (5 μmol/g) in the gray matter of the spinal cord. Applied ionophoretically to mononeurons or interneurons it produces an inhibitory hyperpolarization that is indistinguishable from the inhibitory synaptic response. Strychnine, a convulsion poison that acts mainly on the spinal cord, blocks both the synaptic inhibitory response and the response to glycine. This, together with direct measurements of glycine release in response to nerve stimulation, provides strong evidence for its physiological transmitter role. Beta-alanine has pharmacological effects and a pattern of distribution very similar to glycine, but its action is not blocked by strychnine. The inhibitory effect of glycine is quite distinct from its role facilitating excitatory responses mediated by NMDA.

The glycine receptor resembles the $GABA_A$ receptors; it is a multimeric ligand-gated chloride channel, of which cloning has identified a number of subtypes. Mutations affecting the receptor have been identified in some inherited neurological disorders associated with muscle spasm and reflex hyperexcitability. There are no therapeutic drugs, which act by modifying glycinergic transmission. Tetanus toxin, a bacterial toxin resembling botulinum toxin, acts selectively to prevent glycine release from inhibitory interneurons in the spinal cord, causing excessive reflex hyperexcitability and violent muscle spasms ("lockjaw"). (Cooper et al, 1996; Lopez et al, 2001; Rang, Dale, Ritter, and Gardner, 2001)

4.2 Excitatory amino acid neurotransmitters

Glutamate is the primary neurotransmitter in the mammalian CNS and has been implicated as a potent neurotoxin. In brain, L-glutamate is synthesized in the nerve terminals from two sources (Figure 2): from glucose via the Krebs cycle and transamination of α-oxoglutarate and from glutamine that is synthesized in glia cell, transported into nerve terminal and locally converted by glutaminase into glutamate. In the glutamate-containing nerve terminal, glutamate is stored in synaptic vesicle, and on depolarization of the nerve terminal, it is released by a calcium-dependent exocytotic process (Dichter and Wilcox, 1997). Glutamate receptor subtypes are distinguishable

by biochemical, electrophysiological, and pharmacological criteria. Multiple receptor gene families mediate the versatile and widespread function of glutamate signaling. Based on their mode of function, glutamate receptors have been divided into two major groups; metabotropic receptors which are couple to second messenger pathway through G-proteins and ionotropic receptors which are ligand-gated ion channels (Chapman, 1998; Dodd et al., 2000; Rang, Dale, Ritter, and Gardner, 2001).

Ionotropic glutamate receptor (GluR)

The ionotropic glutamate receptor (GluR) family is composed of closely related subunits that combine to form receptors that are selectively activated by agonists. These receptors allow the flow of ions across the neuronal membrane. The ionotropic glutamate receptors can be further divided into three major groups according to their respective preferential activator namely N-methyl-D-aspartate (NMDA), α-amino acid-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid (KA) (Chapman, 1998). The KA and AMPA receptors share many characteristics and are collectively refer to as the non-NMDA receptors. Glutamate binds to all these receptors. The NMDA receptor binds NMDA or glutamate; the AMPA receptor binds AMPA, KA or glutamate; the KA receptor binds KA or glutamate. Binding of an agonist to any of these glutamate receptor subtypes leads to a conformation change in the ionic channel linked to the receptor with subsequent flow of cations into the neuron. Channels of the NMDA receptor allow influx of Na^+ and Ca^{2+} ions while AMPA and kainate receptors admit Na^+ (and to a lesser exert extent Ca^{2+}) ions. (Chapman, 1998; Dodd et al, 2000)

The NMDA receptor channel has slower kinetics than AMPA/KA receptors and mediates Na^+ and Ca^{2+} influx. The slow kinetics of channel opening allows both summation of glutamate response and a large influx of calcium into cell. Increase in intracellular calcium concentration is believed to be critical for many of the proposed role of the NMDA receptor. Ion flux through the NMDA receptor is voltage dependent. When the cell is at resting potential, Mg^{2+} binds within the ion channel and block the cation flux. It is likely that synaptically release glutamate first activates AMPA/KA receptors, thereby causing depolarization of the post-synaptic cell and

release of Mg^{2+} ion such that other cations can move through the NMDA receptor ion channel. (Chapman, 1998; Dodd et al, 2000)

Metabotropic receptor (mGluR)

To date, there are eight metabotropic glutamate receptors (mGlu1-8) with known molecular sequence and can be studied in expression system. Many of the effects mediated by diacylglycerol or cAMP are related to alter phosphorylation of various enzymes receptors or transporters that give rise to prolonged function changes. Activation of Group I (mGlu 1 and mGglu5) receptors can potentiate NMDA and AMPA response. Glutamate release can be enhanced by mGlu1 activation. GroupII (mGlu2 and mGlu3) and Group III (mGlu4, mGlu6, mGlu7, and mGlu8) receptors act presynaptically to decrease glutamate release. (Chapman, 1998; Wong et al, 1999;Dodd et al, 2000;Najm et al, 2000; Rang, Dale, Ritter, and Gardner, 2001)
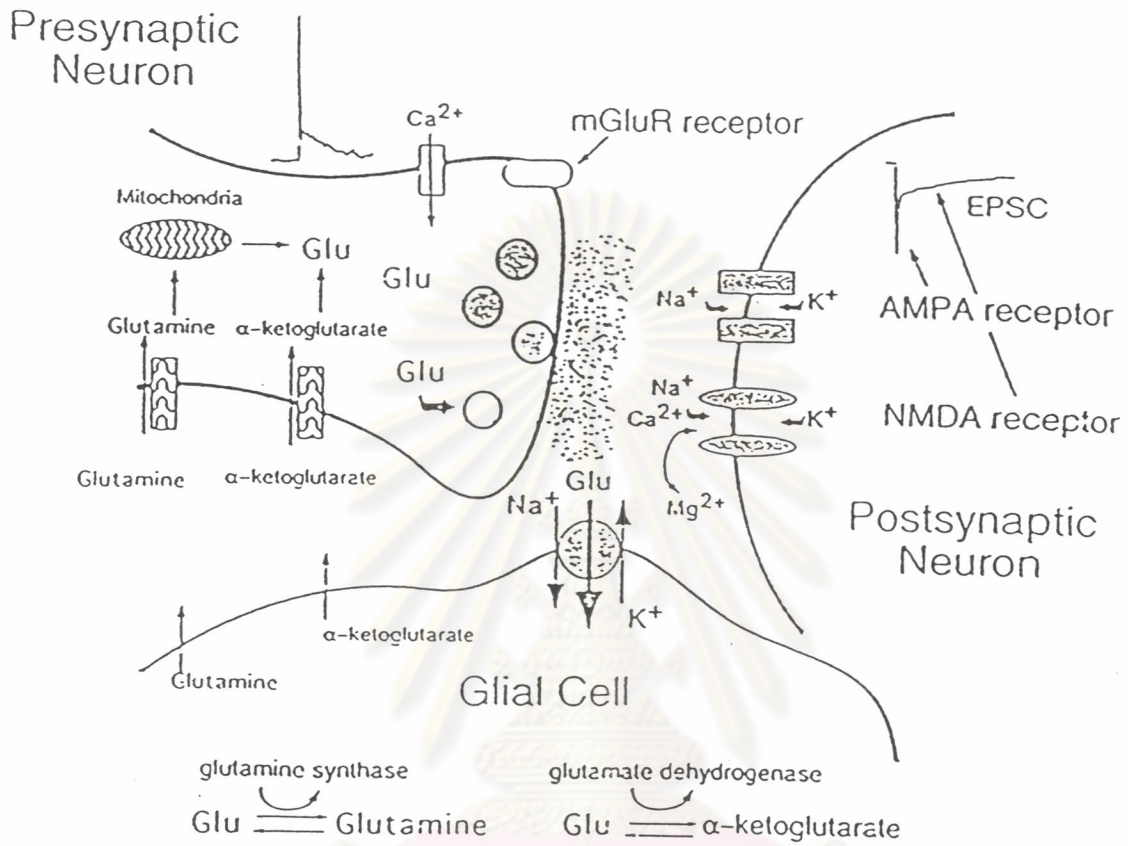
Figure 2 Schematic diagram of Glutamate

(From Dichter and Wiicox, 1997)

5. Therapy of Epilepsy

Therapy should be directed toward the cause of the seizures, if known. Seizures associated with metabolic and systemic disorders usually respond poorly to anticonvulsants but cease with correction of the underlying abnormality. Acute withdrawal from alcohol and other sedative drugs produces self-limited seizures that, in general, require no anticonvulsant drug therapy. Acute head trauma and other structural brain lesions that result in seizures must be rapidly diagnosed and treated, and the associated seizures controlled by anticonvulsant drug therapy. Idiopathic epilepsy is treated with anticonvulsant medications. (Simon, Aminoff, and Greenberg, 1999)

5.1 Surgical treatment of epilepsy

Surgical intervention should be considered when seizures fail to respond to antiepileptic drugs and when they continue to disrupt patient quality of life. Advances in surgical techniques and improved method, of it identifying epileptogenic brain areas have made surgical treatment an option for more patients with uncontrolled seizures today than ever before. In 1985 for example, there were about 500 operations for epilepsy in the United States; in 1990, there were more than 1500, and in 1998 nearly 5000.

In the past, there was considered disagreement about when to refer patients for surgery, and many recently, the average time from epilepsy diagnosis to operation was about 20 years. Currently, increasingly numbers of neurologists believe that it is possible to identify patients who are likely to benefit from surgery earlier in the course of their illness, and that minimizing the delay between onset of seizures and successful intervention provides better seizure control, psychosocial outcome, and quality of life. (Boiling and Oliver, 1998; Pedley, 2000)

Few patients benefit from further attempts at medical treatment if seizures are not controlled with two trials of high-dose monotherapy using appropriate drugs and one trials of rational combination therapy. These steps can be accomplished

within 1 to 2 years. At that point, the detrimental effects of continued seizures, often exacerbated by drug toxicity, warrant referral to a specialized epilepsy center.

The most common type of epilepsy surgery, and the one with which there is the greatest experience, is focal cortical resection. Surgery should be considered for any patient with focal seizures whose attacks remain disabling despite optimal medical therapy. Three criteria identify the ideal patient for resection surgery: (1) the seizures began in an identifiable and localized area of cortex; (2) the surgical excision can encompass the epileptogenic region; and (3) the required resection dose not impaired neurological function. These requirements are met most often by patients with temporal lobe epilepsy or other focal epilepsies associated with a demonstrable cerebral lesion (e.g., cavernous malformation, gangliogliomas). Over 70% of such patients become seizure-free, and about 90% have sufficiently fewer seizures to substantially improve their quality of life. The outcome is less favorable for patients undergoing nonlesional extra temporal resection: about 45% of patients become seizure-free; another 35% have worthwhile improvement. (Ben-Menachem, 2001;Pedley, 2002)

5.2 Selection of Antiepileptic Drugs

The treatment of epilepsy has three main objectives: (1) to eliminate seizures or reduce their frequency to the maximum extent possible, (2) to avoid chronic drug-related adverse effect, and (3) to assist the patient in maintaining or restoring normal vocational and psychosocial adjustment. Although each of these goals is possible, no available medical treatment can permanently eliminate ("cure") epilepsy. Furthermore, less than 50% of adults treated for chronic partial and secondarily generalized seizures become seizure-free for more than 12 months with currently available drugs. (Pedley, 2002)

It should perhaps not be surprising that there might be several mechanisms whereby antiepileptic drugs exert their anticonvulsant effects. In order to discuss actual, as well as potential, mechanisms of action, it is necessary to briefly consider the pathophysiological of epilepsy.

In epilepsy certain neurons and groups of neurons become hyperexcitable and begin firing bursts of action potentials that propagate in a synchronous manner to other brain structures. There may be abnormalities in the neuronal membrane stability of "epileptic neurons" or in their connections with other neurons. It is known that the epileptic bursts consist of sodium-dependent action potentials as well as a calcium-dependent depolarizing potential. Much investigation has centered around the capacity of known anticonvulsant drugs to interact with ion channels, and it is now established that several agents appear to be exerting their effects primarily by inhibiting ion channels. Modulation of neuronal sodium channels decrease cellular excitability and decreases the propagation of nerve impulses. Inhibition of sodium channels appears to be a major component of the mechanism of action of several anticonvulsant drugs, including phenytoin, carbamazepine, and lamotrigine. Much current interest is also centered on the role of calcium channels since the depolarization associated with burst firing is mediated by the activation of calcium channels. At therapeutically relevant concentrations, the antiabsence drug, ethosuximide, appears to exert its effect by inhibiting the T-type calcium channels. (Craig, 1997)

Disinhibition also may play an important role in the generation of epileptic seizures. It has been shown that a reduction of GABAergic inhibition is necessary to produce the synchronous burst discharges in groups of cells. Compounds that antagonize the activity of GABA (picrotoxin, penicillin G and bicuculline) are CNS convulsants while agents that facilitate GABA's inhibition have anticonvulsant activity. Several currently available anticonvulsant drugs act to facilitate the actions of GABA.

Excitatory neurotransmitter may also be involved in epilepsy since it appears that the bursting activity typically seen during epileptic discharges may be due, in part, to the action of glutamate activity on NMDA receptor channels to produce depolarization. Although glutamate antagonists, particularly those that antagonize glutamate at NMDA receptors, have anticonvulsant properties, compounds presently available are much too toxic for human use. (Craig, 1997)

The mechanism of most antiepileptic drugs can be categorized as affecting either ion channels or excitatory neurotransmission. The ion channels affected included the sodium and calcium channels. Increases in inhibitory neurotransmission affect CNS concentrations of GABA, whereas effects to decrease excitatory neurotransmission are focused primarily on glutamate and aspartate. AEDs that are effective against generalized tonic-clonic and partial seizures probably reduce sustained repetitive firing of action potentials by delaying recovery of sodium channels from activation. Drugs that reduce T-type calcium currents are effective against generalized absence seizures. Myoclonic seizures respond to drugs that enhance $GABA_A$ receptor inhibition. (Graves and Garnett, 1999; Stringer, 1999)

With optimal drug therapy, epilepsy is controlled completely in about 75% of patients, but about 10% (50,000 in Britain) continue to have seizures at intervals of 1 month or less, which severity disrupts their life and work. There is therefore a need to improve the efficacy of therapy. (Rang, Dale and Ritter, 1999)

New antiseizure drug are being sought that act by one of three mechanisms: (1) enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, and (3) modification of ionic conductances. (Porter and Meldrum, 2001)

Newer Antiepileptic Drugs

For about 25 years, from the mid-1960s, the inventiveness of the pharmaceutical industry in producing improved antiepileptic drugs dried up. New drugs began to appear from 1990 onwards, the motivation being that existing antiepileptic drug therapy failed to achieve control of seizures in about 25% of cases, and was limited by unwanted effects. Several of these newer drugs one new in use, and more are under evaluation. (Rang, Dale and Ritter, 1999)

There are at least three preclinical strategies which are used for development of new anticonvulsant drugs (1) random screening of newly synthesized chemical compounds of diverse structural categories for anticonvulsant activity in

animal model, (2) structural variation of known anticonvulsant drugs and (3) mechanism-based rational drug development, based on knowledge of the basic pathophysiological events involved in seizures or epilepsy (Lösher and Schmidt, 1994 and Upton, 1994). All three strategies have generated clinically effective anticonvulsant drugs, although many scientists currently believe that the strategies of rational ("modern") drug development have important advantages over the more traditional strategies.

The most important strategies of rational design of anticonvulsant drugs have been (1) enhancement of GABA-mediated neuronal inhibition, (2) diminution of glutamate-mediated neuronal excitation and (3) modulation of Na^+, K^+ and particularly Ca^+ ion channels (Lösher and Schmidt, 1994 and Upton, 1994).

Vigabatrin

Vigabatrin, the first "designer drug" in the epilepsy field, is a γ-vinyl-substituted analogue of GABA that was designed as inhibitor of the GABA metabolizing enzyme, and works by forming an irreversible covalent bond. In animal studies, vigabatrin increases the GABA content of the brain, and also increases the stimulation-evoked release of GABA, implying that GABA-transaminase inhibition can increase the releasable pool of GABA and effectively enhance inhibitory transmission. In humans, vigabatrin increases the content of GABA in the CSF. Although its plasma half-life is short, it produces a long-lasting effect, because the enzyme is blocked irreversibly, and so can be given by mouth once daily. Evidence of neurotoxicity was found in animals, but has not been found in humans, removing one of the main question marks hanging over this drug.

The main drawback of vigabatrin is the occurrence of depression, and occasionally psychotic disturbances, in a minority of patients, otherwise it is relatively free from side effects.

Vigabatrin has been reported to be effective in a substantial proportion of patients resistant to the established drugs, and may represent an important therapeutic

advance (Rang, Dale and Ritter, 1999; McLachlan, 2000; Trescher and Lesser, 2000;Sabers and Gram, 2000;McNamara, 2001; Brunbech and Sabers, 2002).

Lamotrigine

Lamotrigine, though chemically unrelated, resembles phenytoin and carbamazepine in its pharmacological effects, acting on sodium channels, and inhibiting the release of excitatory amino acids. It appears that, despite its similar mechanism of action, lamotrigine has a broader therapeutic profile than the earlier drugs, with significant efficacy against absence seizures. Its main side effects are nausea, dizziness and ataxia, and hypersensitivity reactions (mainly mild rashes, but occasionally more severe). Its plasma half-life is about 24 hours, with no particular pharmacokinetic anomalies, and it is taken orally (Rang, Dale and Ritter, 1999; McLachlan, 2000; Trescher and Lesser, 2000; Sabers and Gram, 2000; McNamara, 2001; Brunbech and Sabers, 2002).

Felbamate

Felbamate is an analogue of an absolute anxiolytic drug; meprobamate. It is active in many animal seizure models, and has a broader clinical spectrum than earlier antiepileptic drugs, but its mechanism of action at the cellular level is uncertain. It has only a weak effect on sodium channels, and little effect on GABA, combined with some inhibition as the facilitatory glycine site of the NMDA receptor. Its acute side effect are mild, mainly nausea, irritability and insomnia, but it occasionally causes severe reactions, resulting in aplastic anemia or hepatitis. For this reason, its recommend use is limited to a form of intractable epilepsy in children (Lennox-Gastaut syndrome) that is unresponsive to other drugs. Its plasma half-life is about 24 hours, and it can enhance the plasma concentration of other antiepileptic drugs given concomitantly (Rang, Dale and Ritter, 1999; McLachlan, 2000; Sabers and Gram, 2000; Trescher and Lesser, 2000; McNamara, 2001; Brunbech and Sabers, 2002).

Gabapentin

Gabapentin was designed as a simple analogue of GABA that would be sufficiently lipid-soluble to penetrate the blood-brain barrier. It turn to be an effective anticonvulsant in several animal models, but, surprisingly, not a GABA –mimetic. It has no effect on any of the major neurotransmitter mechanism, or on sodium or calcium channels, but binds with high affinity to a specific site in the brain, which appears to be the amino acid transporter system that occurs in many neurons and other cells. The mechanistic implications of this are unknown, and its mode of action remains an intriguing mystery. The side effects of gabapentin (mainly sedation and ataxia) are less severe than with many antiepileptic drugs. The absorption of gabapentin from the intestine depends on the amino acid carrier system, and shows the properly of saturability, which means that increasing the dose do not proportionately increase the amount absorbed. This makes gabapentin relatively safe, and free side effects associated with overdosing. Its plasma half-life is about 6 hours, requiring dosing two to three time daily. It is free of interactions with other drugs. Efficacy in patients resistant to conventional drugs has been claimed, but the clinical role of gabapentin remains to be established (Rang,Dale and Ritter, 1999; McLachlan, 2000; Sabers and Gram, 2000;Trescher and Lesser, 2000;McNamara, 2001; Brunbech and Sabers,2002).

Tiagabine

Tiagabine, an analogue of GABA, which is able to penetrate the blood-brain barrier, acts by inhibiting GABA uptake, and was product of rational drug design. It binds selectively to one of the four known molecular subtypes of the GABA transporter, which is expressed in both neurons and glial cells. It enhances the extracellular GABA concentration, as measured in microdialysis experiments, and also potentiates and prolongs GABA-mediated synaptic responses in the brain. It has a short plasma half-life, and its main side effects are drowsiness and confusion. The clinical usefulness of tiagabine has not yet been fully assessed (Rang, Dale and Ritter, 1999; McLachlan, 2000; Sabers and Gram, 2000; Trescher and Lesser, 2000; McNamara, 2001; Brunbech and Sabers, 2002).

Topiramate

Topiramate is a recently introduced drug, which mechanistically appears to do a little of everything, blocking sodium channels, enhancing the action of GABA, blocking AMPA receptors and, for good measure, weakly inhibiting carbonic anhydrase. Its spectrum of action resembles that of phenytoin, and it is claimed to produce less severe side effects, as well as being devoid of the pharmacokinetic properties that cause trouble with phenytoin. Its main drawback is that (like many antiepileptic drugs), it is teratogenic in animals, so it should not be used in woman of childbearing age. Currently, it is recommended for use as add-on therapy in refractory cases of epilepsy. (Rang,Dale and Ritter, 1999; McLachlan, 2000; Sabers and Gram, 2000;Trescher and Lesser, 2000;McNamara, 2001; Brunbech and Sabers, 2002)

Zonisamide

Zonisamide was developed in the 1980s in Japan, where it is now licensed. Its mode of action may involve inhibition of voltage-dependent sodium channels, T-type calcium channels, and carbonic anhydrase. It is absorbed rapidly, is less than 50% protein bound, and is eliminated partly by renal excretion and partly by metabolism with a half-life of about 60 hours. Shorter half-life (about 30 hours) is observed in patients taking enzyme-inducing anticonvulsants. Zonisamide is effective against partial seizures and probably various generalized seizure types. Promising results have been reported in progressive myoclonic epilepsy. Maintenance dosage is usually 200 to 600 mg per day in adults and 4 to 10 mg/kg per day in children, given as one or two daily doses. Side effects include somnolence, ataxia, anorexia, confusion, mental slowing, nervousness, fatigue, dizziness, headache, weight loss, and skin rashes. Nephrolithiasis has been described in initial studies in the United States, but it does not appear to have been a problem in Japan. (Perucca, 2000)

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that is absorbed rapidly, is over +0% bound to plasma proteins, and is eliminated unchanged in urine. Its distribution half-life is about 2 hours, whereas elimination half-life is 12 to 15 hours. The

efficacy of acetazolamide in epilepsy has not undergone adequate, controlled evaluation, but the drug is considered to be of value against various seizure types and especially against absence seizures. Dosage usually ranges between 3 and 20 mg/kg per day. Since efficacy may be limited by development of tolerance, acetazolamide has been proposed for intermittent use, especially in conditions such as catamenial epilepsy. Possible adverse effects include sedation, fatigue, depression, paresthesias, sexual dysfunction, anorexia, weight loss, hypokalemia, nephrolithiasis, skin rashes, and other hypersensitivity reactions. Acetazolamide should be used cautiously and at lower dosages in the elderly and wherever inhibition of carbonic anhydrase is undesired. Acetazolamide may decrease the serum levels of primidone and increase those of carbamazepine. Potentiation of acetazolamide toxicity by salicylates may occur. (Perucca, 2000)

Nonpharmacologic therapies

Vagus nerve stimulation

Approved in 1997, the vagus nerve stimulator is the first device approved for the treatment of epilepsy. The device consists of a fully implantable pulse generator and an electrode that attaches to the left vagus nerve. Stimulation parameters are adjusted according to patient tolerance and seizure control. Usually the device is programmed for stimulations lasting 30 seconds, followed by 5 minutes of off time, with this pattern repeating continuously while the device is in operation. There is also a hand-held magnet that can be used to manually activate the device to deliver stimulation. This latter feature is used by some patients to abort seizures at the time their seizure era begins. The vagus nerves stimulator is approved for use in adults and adolescents as adjunctive treatment (with AED therapy) for partial-onset seizures that do not respond to drug therapy. In clinical trials, use of vagus nerve stimulator reduces the frequency of seizures by 50% or more in 25% of patients. This response is comparable to many of the newer AEDs such as gabapentin and tiagabine. Therapeutic benefits from vagus nerve stimulation are maintained for up to 5 years (and possibly longer) with continued use of the device. Preliminary evidence also supports the efficacy of vagus nerve stimulation in

children and in patients with medically refractory generalized-onset seizures; however, more study is needed to confirm these observations. The most common adverse effects associated with used of the vagus nerve stimulator are hoarseness, coughing and throat discomfort during the stimulation burst. (Alldredge, 2000)

Ameltolide

Ameltolide [4-amino-N- (2,6-dimethylphenyl) benzamide, LY 201116, ADD 75073 and compound 8 in Clark et al. (1985)] is a newly discovered and described anticonvulsant agent (Clark, 1988; Leander et al., 1988). Ameltolide is very selective for blocking the tonic extensor response in the maximal electric shock (MES) seizure test, without significant activity in the chemical-convulsing threshold test, subcutaneous (S.C.) pentylenetetrazol (PTZ), bicuculline (BIC), and picrotoxin, and the tonic extensor strychnine test (Clark, 1988). The anticonvulsant effect in the MES test occurs at significantly lower dose than that produce neurological impairment (rotarod or horizontal screen, HS) or produce other signs of toxicity (Clark, 1988; Leander et al., 1988). Also, ameltolide does not produce any sign of tolerance with daily administration, and it does not interact with the hypnotic effects of hexobarbital after either acute or chronic administration (Leander et al., 1988). This profile of preclinical anticonvulsant activity is similar to those of phenytoin (PHT) and carbamazepine (CBZ). Unfortunately, ameltolide was rapidly metabolically inactivated by N-terminus and subsequent hydroxylation of one of the methyl substitute. However, following the pioneering discovery of ameltolide, it has become one of a fruitful compound for designing of several new and potent anticonvulsants. (Robertson et al., 1991)
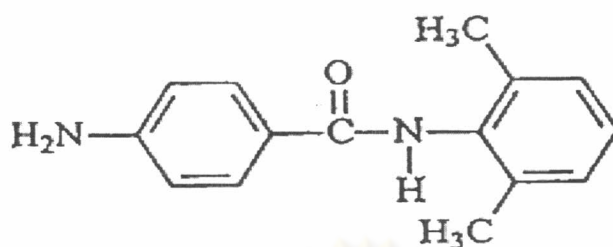
Figure3. Structural of ameltolide

Pharmacology of ameltolide

Ameltolide was a potent and selective anticonvulsant in the maximal electroshock (MES) test. (AntiMES activity: $ED_{50}=2.6$ mg/kg, i.p. in mice; $ED_{50}=3.9$ mg/kg, orally in mice; $ED_{50}=32.5$ mg/kg, orally in rats). Ameltolide was similar to PHT in that it did not offer protection against seizures induced by pentylenetetrazol, bicuculline, picrotoxin or strychnine. The anticonvulsant profile of ameltolide is similar to those of phenytoin and carbamazepine. Such a profile of activity has been described as"preventing seizure spread" rather than "raising seizure threshold". The anticonvulsant effect in the MES test occurs at dose significantly lower than produce neurological impairment (rotarod test; $TD_{50}=15$ mg/kg, i.p. in mice; 38.3 mg/kg, orally in mice, 458.9 mg/kg, orally in rats), and well beyond those that impair the righting reflex ($HD_{50}=43.8$ mg/kg, i.p. in mice) or produce lethality ($LD_{50}=160$ mg/kg, i.p. in mice). (Clark, 1988; Leander et al, 1988 and Swinyard et al, 1989)

By considering the values of ED_{50}, TD_{50}/ED_{50}, LD_{50}/HD_{50}, LD_{50}/TD_{50} and TD_{3}/ED_{97}, the anticonvulsant activity and neurotoxicity of ameltolide compare favorably with those of prototype anticonvulsants in the same assays (Table2-5). Ameltolide produces no sign of tolerance with daily administration, and dose not interacts with the hypnotic effects of hexobarbital after either acute or chronic administration. All of these

results suggest that ameltolide will be an effective anticonvulsant in humans and support development of the compound for the treatment of epilepsy. (Clark, 1988; Leander et al, 1988 and Swinyard et al, 1989)

Table 2 Minimal neurotoxicity and anticonvulsant potency of intraperitoneally
administered ameltolide and some prototype antiepileptic drugs in mice

Substance	Time of test[a] (hr)	Rotarod TD_{50} (mg/kg)	ED_{50} (mg/kg) and PI				
			MES	sc.PTZ	sc.BIC	sc.PIC	Sc.Strych
ameltolide	½, ½	15.0	[5.80] 2.6	[<0.75]	[<0.75]	[<0.5]	[<0.75]
PHT	2, 2	65.5	[6.89] 9.5	[<0.22]	[<0.65]	[<0.65]	Maximum Protection
PB	½, 1	69.0	[3.17] 21.8	[5.24] 13.2	[1.83] 37.7	[2.51] 27.5	-
ESM	½, ½	441	[<0.44]	[3.38] 130	[0.96] 459	[1.82] 243	-
VPA	¼, ¼	426	[1.5] 272	[2.87] 149	[1.18] 360	[1.10] 387	[1.45] 293

PHT, phenytoin; PB, Phenobarbital; ESM, ethosuximide; VPA, valproate; TD_{50}, dose
eliciting evidence of minimal neurotoxicity in 50 % of animals; ED_{50} , dose required to
produce the desired endpoint in 50 % of animals; MES, maximal electroshock seizure;
sc. PTZ, subcutaneous pentylenetetrazole; sc. BIC, sc. Bicuculine; sc. PIC, sc.
Picrotoxin; sc. Strychine; Protective index (PI = TD_{50}/ ED_{50}) in boxes.

[a]First number, TD_{50}; second number, ED_{50}

Table 3 Minimal neurotoxicity and anticonvulsant potency of orally administered ameltolide and some prototype antiepileptic drugs in mice

Time of test [a] (test)			TD_{50} (mg/kg)		MES ED_{50} (mg/kg)		Sc. PTZ ED_{50} (mg/kg)	
Substance	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
ameltolide	½, 1	2,1	38.3	458.9	[9.8] 3.9	[14.1] 32.5	[<0.5]	[<0.9]
PHT	2, 2	½, 4	86.7	No ataxia up to 3,000	[9.59] 9.04	[>100] 29.8	[<0.29]	NA
PB	2< 2	½, 5	96.8	61.1	[4.82] 20.1	[6.68] 9.14	[7.69] 12.6	[5.29] 11.6
ESM	1,1/2	2, 2	879	1,012	[<0.44]	[0.84]	[4.56] 193	[18.8] 54
VPA	2, 1	1, ½	1,264	280	[1.90] 665	[0.57] 490	[3.26] 388	[1.56] 180

PHT, phynotoin; PB, phenobarbital; ESM, ethosuximide; VPA, valproate; TD_{50}, dose eliciting evidence of minimal neurotoxicity in 50% of animals; ED_{50}, dose required to produce the desired endpoint in 50% of animals; MES, maximal electroshock seizure; sc. PTZ, subcutaneous pentylenetetrazol; Protective index (PI = TD_{50}/ED_{50}) in boxes; NA, not applicable

[a]Toxicity, MES and sc. PTZ, respectively.

Table 4. Quantitative toxicity profile of intraperitoneally administered ameltolide and
some prototype antiepileptic

Substance	Time of test[a] (hr)	Dose (mg/kg)		
		Lethality (LD_{50})	Righting reflex (HD_{50})	Rotorod (TD_{50})
ameltolide	24, ½, ½	160.8	[3.67] 43.8	[10.71] 15.0
PHT	24,12, 2	230	[1.29] 178	[3.51] 65.5
ESM	24, ½, ½	1,752	[2.06] 851	[3.98] 441
VPA	24, ¼, ¼	1,105	[1.25] 886	[2.59] 426

PHT, phenytoin; PB, phenobarbital; ESM, ethosuximide; VPA, vapoate; LD_{50}, dose that
cause death in 50% of animals, HD_{50}, dose at which 50% of animals lost righting reflex;
TD_{50}, dose eliciting evidence of minimal neurotoxicity in 50% of animals. Ratio LD_{50}/HD_{50}
or $LD_{50}/TD50_{50}$ in boxes.
[a]Lethality, righting reflex, and rotorod, respectively.

Table 5. Safety ratios (TD_3/ED_{97}) of ameltolide, PHT, PB, and VPA

Substance	Spices and route of administration	Parameter		
		TD_3 (mg/kg)	MES ED_{97}	Ratio
ameltolide	Mice, i.p.	9.8	6.0	1.6
	Mice, oral	23	9.1	2.5
	Rats, oral	230	47	4.9
PHT	Mice, i.p.	49	13.5	3.6
	Mice, oral	185	62	3.4
	Rats, oral	NA	95	
ESM	Mice, i.p.	59	29	2.0
	Mice, oral	58	46	1.3
	Rats, oral	14	26	0.5
VPA	Mice, i.p.	345	380	0.9
	Mice, oral	500	850	0.6
	Rats, oral	115	1800	0.1

PHT, phenytoin; phenobarbital; ESM, ethosuximide; VPA, valproate; NA, not applicable.

[a]Ratio<1 indicate that 97% protection is obtained only with some minimal neurotoxicity.

[b]TD3, dose eliciting evidence of minimal neurologic toxicity in 3% of animals; ED_{97}, dose required to produce anti-MES activity in 97% of animals.

Mechanism of action of ameltolide

Up to now, the mechanism of action of ameltolide is still remains unknown. It is expected to exert anticonvulsant activity by blocking sodium channels according to its phenytoin-like profile and it specifics only in MES test. This hypothesis was supported by the experiment of Vamecq's team that reported a correlation between interaction with the neuronal voltage-dependent sodium channel and anticonvulsant activity of ameltolide in the MES test. (Potts et al., 1989 and Vamecq et al., 1998)

Metabolism, Disposition, and Pharmacokinetics of ameltolide

The metabolism, disposition, and pharmacokinetics of ameltolide have been studied in rats. C-ameltolide was absorbed (~94%) from the gastrointestinal tract following oral administration. Of the dose administered, 64.5% was exerted in the urine and 29% in the bile; with the majority being excreted during the first 24 hr. Peak plasma levels of ameltolide were observed at 0.75 hr, whereas peak plasma concentrations of radioactivity were seen at 2 hr after dosing. Maximum levels of radioactivity were observed at 2 hr in all of the tissue studied. The elimination of radioactivity from the tissue was monophasic with a mean half-life of 3.4 hr. Quantitating and isolating metabolites from urine and plasma investigated biotransformation of ameltolide in rats. The major route of metabolism was N-acetylation to form 4-(acetylamino)-N-(2,6-dimethylphenyl)benzamide (LY201979,XXVII), and then subsequent hydroxylation to from 4-(acetylamino)-N-(2-hydroxymethylmethyl-6-methylphenyl)benzamide(LY272546, XXVIII). Two hours after oral dosing with ^{14}C-ameltolide, XXVII and XXVIII comprised 92% of the total radioactivity in the plasma. The major urinary metabolic, accounting for 63% of the radioactivity in the urine, was XXVIII.

Pharmacological studies demonstrated that N-acetylation followed by hydroxylation of one of the benzylic methyl groups result in virtually complete metabolic inactivation of ameltolide. XXVII can be metabolized back to ameltolide in a variety of species whereas XXVIII cannot be converted back to its parent compound. (Potts, Gabriel and Parli, 1989; Robertson et al., 1991; Leander et al., 1992)

Analogues of ameltolide

In1994, N- (*p*-aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline was synthesized by Sathit Niratisai as the rigid analogue of ameltolide (Sathit Niratisai, 1994). The preliminary result indicated that it exhibit anticonvulsant activity against MES test. However, its synthetic approaches are complicate with several steps.

To extend the structure activity relationship on N-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroquinoline phamacophore and to improve the synthetic procedures, herein, N-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroquinoline(CU-17-02)and derivatives with substitute on 1,2,3,4- tetrahydroquinoline ring were synthesized by simpler methods, and expected to possess anticonvulsant activity certainly, the introduction of methyl group along the variable position of 1,2,3,4- tetrahydroquinoline nucleus especially at the piperidine ring and C-8 (see Table 6) will affect the conformational orientation of the target compounds. These data may lead to an understanding of an appropriate conformational structure of this series for target binding site in the future study. In addition, steric hindrance in the same compounds may affect the metabolic hydroxylation, which may in turn change the potency or duration of anticonvulsant activity. The chemical structure of target compound is illustrated in Table 6.

Table 6 Structures of N-(*p*-aminobenzolyl)-1,2,3,4-tetrahydroquinolines to be

synthesized
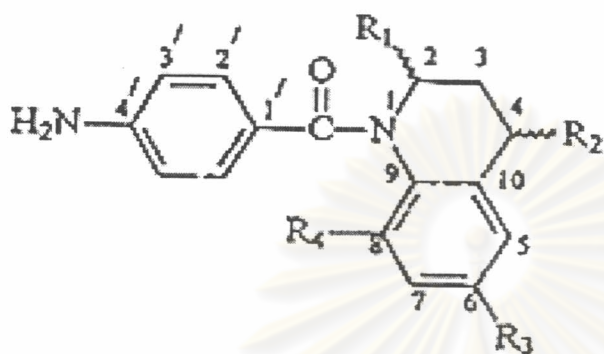
	substitute			
	R_1	R_2	R_3	R_4
CU-17-02 (4a)	H	H	H	H
CU-17-04 (4b)	CH_3	H	H	H
CU-17-06 (4c)	H	CH_3	H	H
CU-17-08 (4d)	H	H	H	CH_3
CU-17-10 (4e)	CH_3	H	F	H
CU-17-12 (4f)	CH_3	H	H	CH_3
CU-17-14 (4g)	H	CH_3	H	CH_3
CU-17-16 (4h)	H	H	H	OMe

CU-17-06 (N-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-4-methylquinoline)

In 2000, N- (*p*-aminobenzoyl)-1,2,3,4-tetrahydroquinoline and its analogues were synthesized by Chamnan Patarapanich and Thanarat Kieatsakol by using ameltolide as prototype agent. The preliminary result indicated that it exhibit anticonvulsant activity against MES test. CU-17-06 (Fig. 4) is one of these analogues and expecting to possess anticonvulsant activity. In addition, it does not have further investigated of ameltolide' s mechanism via neurotransmitter system (such as GABA, glycine, aspartate, and glutamate) by microdialysis technique.
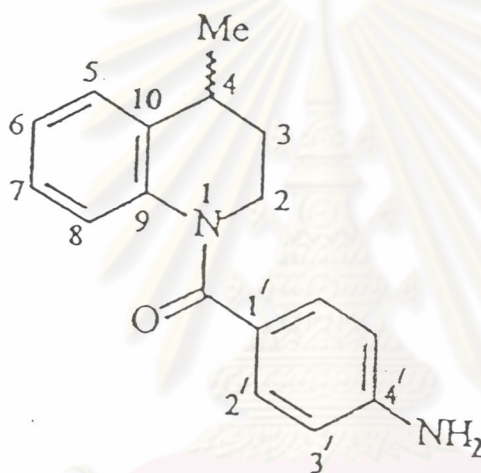

Figure 4. Structural of CU-17-06

The main purpose of this study was to evaluate anticonvulsant effect of CU-17-06 in several animal models of epilepsy as well as its adverse effects and acute toxicity. Furthermore a possible effect of CU-17-06 on the levels of cortical excitatory and inhibitory acid neurotransmitters of freely moving rats would also be investigated.