Chapter II

Review Literature

Seizures

Seizures are time-limited paroxysmal event that result from abnormal, involuntary, rhythmic neuronal discharges in the brain. Seizure are usually short, lasting less than 5 minutes, but can be preceded by a prodromal phase and followed by a long postictal phase, during which there is gradual return to baseline. Seizure usually end spontaneously without intervention. Except status epilepticus is a life-threatening medical emergency (Shneker and Fountain, 2003).

Epilepsy

Epilepsy is a disease characterized by spontaneous recurrence of unprovoked seizures. Seizures and epilepsy are different disorders, and the terms should not be used interchangeably. It is not accurate to refer to seizures as epilepsy, although "seizure disorder" refers to epilepsy. Seizures are symptoms, whereas epilepsy is a disease characterized by recurrent seizures (Shneker and Fountain, 2003).

1. Causes of seizure and epilepsy

Seizures are spontaneoused or provoked. Spontaneoused seizures occur in persistent brain disease, ie, epilepsy. Provoked seizures are triggered by certain factors in an otherwise healthy brain, eg, acute metabolic processes, acute neurologic insult, drugs, and excessive physiologic conditions. Common provoking factors are listed in Table 1.

Table1. Common causes of provoked seizure. (Shneker and Fountain, 2003).

- Metabolic abnormalities
  - Hypoglycemia and hyperglycemia
  - Hyponatremia
  - Hypocalcemia
- Alcohol withdrawal
- Acute neurological insult
  - Infection (meningitis, encephalitis)
  - Stroke (ischemic, hemorrhagic)
  - Head trauma
- Illicit drugs intoxication and withdrawal
- Prescribed medication that lowers seizure threshold
  - Theophylline
  - Tricyclic antidepressent
  - High fever in children
  - Epilepsy

Any process that causes alteration of the structure or function of cerebral neurons predisposes to epilepsy (Table 2).

Table2. Structural brain diseases that predispose to epilepsy. (Shneker and Fountain, 2003).

Congenital
Heterotopias
Cortical dysphasia
Degenerative
Alzheimer disease
Infectious
Meningitis
Encephalitis
Abscess
Trauma
Tumor
Vascular
Vascular malformation
Stroke
Subarachnoid hemorrhage

In population-based studies the cause of epilepsy was due previous brain insult eg. cerebrovascular disease, head trauma and brain tumor (Hauser, Annegers and Kerland, 1991; Anneger, Rocca and Hauser, 1996).

2. Classification of seizures and epilepsy

The classification was standardized with adoption of the International League Against Epilepsy (ILAE) Classification of epileptic seizures, in 1981, (Dreifuss et al., 1981).

ILAE Classification of epileptic seizures

The International League against Epilepsy (ILAE) classification (1981) of human epilepsy divided seizures into partial, generalized and unclassified subtypes (Dreifuss et al, 1981).

This distinction is important because each seizure type present with different symptoms and responds to different treatment. Seizures are classified primarily on the basis of symptoms observed during the seizure. Generalized seizures are characterized by complete loss of consciousness at onset of the seizure, because the entire cortex is involved. Partial seizures are characterized by retention of consciousness, because they begin a limited brain region.

Table 3. Modified ILAE classification of seizures (Dreifuss, 1981).

- Partial seizures
  - Complex partial seizures
  - Simple partial seizures
    - Motor
    - Sensory
    - Autonomic
    - Psychiatric
  - Secondary generalized tonic-clonic seizures
- Generalized seizures
  - Tonic-clonic (primary tonic-clonnic)
  - Absence
  - Myoclonic
  - Clonic
  - Tonic
  - Atonic
  - Atypical absence
  - Infantile spasm

3. Amino acid neurotransmitters

Several amino acids have gained recognition as major neurotransmitter candidates in the mammalian Central nervous system (CNS).

On the basis of neurophysiological studies, amino acids have been separated into two general classes: excitatory amino acids (glutamic acid, aspartic acid, cysteic acid, and hemocysteic acid), which depolarize neurons in the mammalian CNS; and inhibitory amino acid (gamma amino butyric acid (GABA), glycine, taurine, and β-alanine), which hyperpolarize mammalian neurons (Cooper et al, 1996).

3.1 Excitatory amino acid neurotransmitter

Glutamate and aspartate occur in uniquely high concentrations in the brain. These appear to play important roles in the initiation, spread and maintenance of epileptic activity, neurodegenerative disease and cerebral ischemia (Faden, Ellison and Noble, 1990; Meldrum, 1994).

Glutamate is the principal excitatory neurotransmitter in the mammalian brain (Meldrum, 2000). Focal injection of glutamate induces seizures in animals, and over-activation of glutamatergic transmission or abnormal glutamate receptor properties are observed in certain experimental seizure models and human epilepsy syndromes (Meldrum, 1995). Inhibition of the neuronal release of glutamate and blocked of its receptors have received considerable attention in the search for novel AEDs (Meldrum, 2000).

Glutamate is synthesized from glutamine by the action of the enzyme glutaminase in glutamatergic neurons (Daikhin and Yudkoff, 2000).

Following synaptic release, glutamate exerts its pharmacological effects on several receptors, classified into ionotropic and metabotropic families. Glutamate is removed from the synaptic cleft into nerve terminals and glial cells by the action of several specific transporters (Meldrum et al., 1999). Glial cells convert glutamate into glutamine by the action of the enzyme glutamine synthetase. Glutamine is subsequently transferred to glutamatergic neurons, completing the cycle (Daikin and Yudkoff, 2000).

Excitatory amino acid receptors

Ionotropic glutamate receptors are comprised of various combinations of subunits forming tetrameric and pentameric arrays. They are classified into three specific subtypes, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA)(Figure 1.), which from ligand-gated ion channels, permeable to Na^{+} and depending on subtype and subunit composition, Ca^{2+} ions (Trist, 2000). The NMDA receptor is further distinguished by having glycine as a co-agonist. The AMPA and kainate subtypes of the glutamate receptor are implicated in fast excitatory neurotransmission, whereas the NMDA receptor, quiescent at resting membrane potential, is recruited during periods of prolonged depolarization.

The metabotropic family of glutamate receptors, also classified into three distinct subtypes (Groups I, II and III), are G-protein linked and

predominantly presynaptic, possibly controlling neurotransmitter release (Meldrum, 2000).

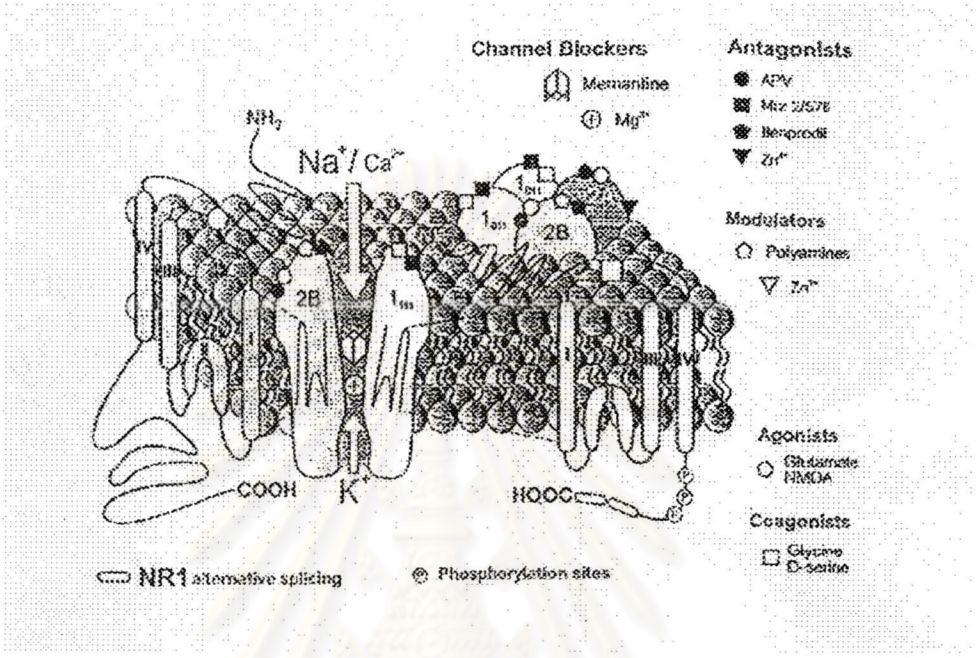

Figure1. Glutamate (NMDA) receptor complex (Danysz and Parsons, 1998).

3.2 Inhibitory amino acid neurotransmitters

3.2.1 GABA

GABA is the major inhibitory neurotransmitter in the CNS and all brain regions. There are two types of inhibitory mechanisms in the CNS,

presynaptic and postsynaptic. In the former, GABA acts on a presynaptic terminal of an excitatory neuron to prevent release of transmitter, this form of inhibition is found predominantly in the spinal cord. Postsynaptic inhibition is the main inhibitory mechanism found in the brain and it is at this site that most of antiepileptic drug exert their action (Davies and Richens, 1993). Impairment of GABA function is widely recognized to provoke seizures, whereas facilitation has an anticonvulsant effect (Loscher, 1999).

Distribution

GABA is found in high concentration in the brain and spinal cord. The ubiquitous distribution of GABA in the brain can account for its utilization as a neurotransmitter in both interneuron and in long-axoned tracts. The interneuron of the cerebral cortex are responsible for regulating the output of cortex and also the activity of the association fibers. The major long-axoned tracts which use GABA as a neurotransmitter are those from the hippocampus to the cortex (Davies and Richens, 1993).

Synthesis and degradation

The major source of GABA in the CNS is most probably glucose entering the tricarboxylic acid (Krebs) cycle via pyruvate and subsequent production of α-ketoglutarate (Figure2). The transamination of α-ketoglutarate produces L-glutamic acid (glutamate), the immediate precursor of

GABA. Fundamental to GABA synthesis is so-called GABA shunt which operates within the terminal of the neuron.

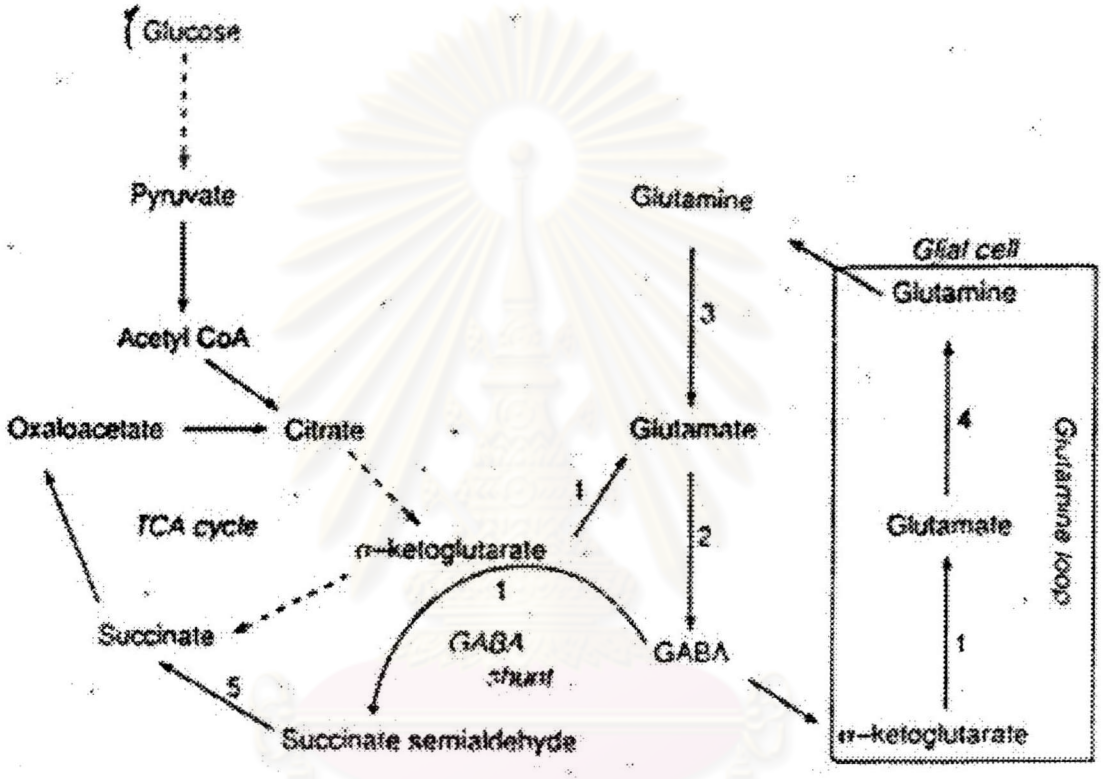

Figure2. Metabolic pathway for the synthesis and degradation of GABA and Glutamate.1: GABA-transaminase; 2: Glutamic acid decarboxylase; 3: Glutaminase; 4: Glutamine synthetase; 5: Succinic semialdehyde dehydrogenase.

GABA is synthesized from glutamate, exclusively in GABAergic neurons by the action of enzyme glutamic acid decarboxylase (GAD) (Loscher, 1999).

GABA receptor

GABA receptors when occupied by the endogenous ligand invariably produce hyperpolarization in the postsynaptic neuron. There are two types of receptor designated as $GABA_A$ and $GABA_B$ (Matsumoto, 1989). $GABA_A$ receptors are the classical bicuculline-sensitive receptors and these which are important in the treatment of epilepsy while the $GABA_B$ receptors are activated by baclofen (Bowery, Hill and Moratalla, 1989). Synaptically stimulation of these results in either pre-or postsynaptic inhibition.

$GABA_A$ receptors originally described as the $GABA_A$/benzodiazepine receptor complex consists of two α and two β subunits (Levitan et al., 1988). However, recent reports indicate that there is a third type of subunit (γ) in the $GABA_A$/ benzodiazepine complex in the brain (Olsen and Tobin, 1990). Activation of $GABA_A$ receptors (Figure 3) opens the chloride channel in the GABA/ benzodiazepine complex and this allows an influx of Cl^- which leads to hyperpolarization of the postsynaptic neuron consequently an inhibition of firing. As this mechanism involves ionic fluxes, it has been termed ionotropic transmission (McGeer et al., 1987).

$GABA_B$ receptor was found at lower levels in the CNS than $GABA_A$ receptor. This receptor has been classified as metabotropic receptor because the transduction mechanism at these sites involved a second messenger resulting in metabolic changes. A linkage of the $GABA_B$ receptor to a G protein (s) is the most probable transduction process (Wojcik, Paez and Ulivi, 1989). Activation of $GABA_B$ receptor leads to a decrease in Ca^{2+} conductance (influx) and/or an increase in K^+ conductance. The latter, producing an efflux of K^+, would lead to hyperpolarization of the neuron. Either of this possibilities would decrease the release of neurotransmitters (Browning, 1991).

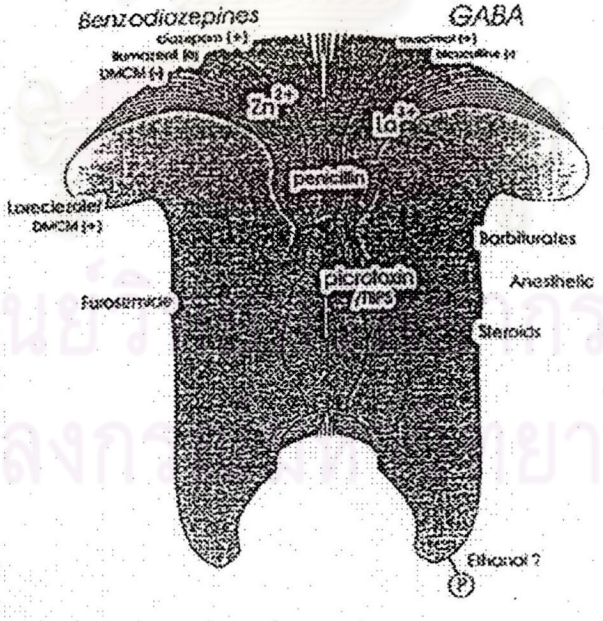

Figure3. The $GABA_A$ receptor-channel complex (Hevers and Luddens, 1998).

3.2.2 Glycine

Distribution

In comparison to other amino acids, glycine is found in relatively high concentration in the spinal cord, displaying higher concentration in spinal gray matter than in the spinal white matter (Cooper, Bloom and Roth, 1991).

Synthesis and degradation

Glycine is synthesized from glucose via glycolytic pathway to produce 3-phosphoglycerate and 3-phosphoserine which is then converted to glycine by a reversible folate-dependent reaction catalyzed by the enzyme serine hydroxymethyltransferase (SHMT). Glycine can also be formed from glycoxylate by transamination (Cooper, Bloom and Roth, 1991; Browning, 1991).

Glycine receptors

Glycine receptors can be classified into two subtypes according to strychnine sensitivity. The strychnine sensitive glycine receptor appears to exist in a macromolecular complex which consists of the glycine recognition site, chloride channel and strychnine binding sites

(Davidoff, 1983; Browning, 1991). Activation of strychnine sensitive glycine receptor, like the $GABA_A$ receptor, cause an increase in chloride conductance which usually results in hyperpolarization and inhibition of postsynaptic membrane, and this effect can be antagonized by strychnine (Davidoff, 1983; McGeer, Eccleg and McGeer, 1988; Browning, 1991). The strychnine-insensitive glycine receptors are linked to the NMDA excitatory amino acid receptor. When compared with the effects of benzodiazepine on the GABA receptor, the enhancement of NMDA response observed with glycine is much greater, suggesting that the main effect of glycine is to prevent desensitization of the NMDA receptor during prolong exposure to agonists. (Cooper, Bloom and Roth, 1991; Browning, 1991).

4. Drugs for treatment of epilepsy

Although the mechanisms of action of the currently marketed AEDs are still not completely understood. At the cellular level, three basic mechanisms are recognized (Meldrum, 1996).

4.1 Enhancement of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission

Several AEDs exert their effects, at least in part, by actions on the GABAergic system. Increased GABA synthesis, increased release, allosteric

receptor facilitation, and reduced inactivation have all been implicated in the mechanisms of action of commonly used agents (Sills et al., 1999). The GABA system also represents the most successful target for the rational design of novel antiepileptic compounds (Loscher, 1998).

Phenobarbital (PB)

The barbiturates have been used since the early 1900s for their sedative, anesthetic, and anticonvulsant properties. PB is still commonly prescribed worldwide for epilepsy, although its cognitive and behavioral side effects have limited its use, particularly in the developed world (Mattson et al., 1985; Brodie and Dichter, 1997).

Benzodiazepines (BZDs)

More than 50 chemically distinct BZDs are marketed worldwide. Diazepam, lorazepam, clobazepam and clonazepam are those most commonly used as AEDs (Brodie and Dichter, 1996). Antiepileptic BZDs have a broad spectrum of clinical activity, with efficacy in the partial and idiopathic generalized epilepsies (Dichter and Brodie, 1996) and for the acute treatment of status epilepticus (Treiman et al., 1998). The development of tolerance to their pharmacological effects has, however, restricted their use in chronic treatment regimens (Brodie and Dichter, 1996).

Vigabatrin

In 1989, vigabatrin (VGB) became the first of the new generation of AEDs to be licensed in the United Kingdom. It was initially approved as adjunctive therapy for partial seizures with or without secondary generalization (Dichter and Brodie, 1996). It has subsequently demonstrated particular efficacy in the treatment of infantile spasms (Appleton et al., 1999).

Tiagabine

Tiagabine (TGB) is a novel AED, recently licensed widely for the adjunctive treatment of partial seizures with or without secondary generalization (Leach and brodie, 1998). It is an analogue of nipecotic acid, a prototypic GABA uptake blocker, which is widely recognized to prevent GABA transport into both neurons and glia cells (Krogsgaard-Larsen et al., 1987). Nipecotic acid, however, fails to cross the blood-brain barrier following systemic administration. This problem is overcome by linking it to a lipophillic anchor to form TGB, which is able to cross the blood-brain barrier more readily (Brodie, 1995).

4.2 Attenuation of excitation (particularly glutamate-mediated) transmission.

Although none of the commonly used AEDs exert their pharmacological effects solely by an action on the glutamate system, blocked of ionotropic glutamate receptors is believed to contribute to the antiepileptic activity of several compounds (Upton, 1994; Macdonald & Kelly, 1995; Meldrum, 1996; White, 1999). In addition, several AEDs have been reported to reduced glutamate release, although this effect may be more indicative of their actions on neuronal Ca^{2+} channels than a direct effect on the glutamate system (Stefani, Spadoni and Bernardi, 1997).

4.3 Modulation of voltage-dependent ion channels (Na^+, Ca^{2+},K^+)

Na^+ channels

In the nervous system, voltage-gated ion channels control the flow of cations across surface and internal cell membranes (Barchi, 1998). Of these, the Na^+channels is arguably of principal importance. Voltage-dependent Na^+ channels are responsible for the upstroke of the neuronal action potential, and ultimately control the intrinsic excitability of the nervous system (Porter and Rogawski, 1992). The neuronal Na^+ channel has a multi-subunit structure that forms a Na^+-selective, voltage-gated pore through the plasma membrane. The

protein structure undergoes conformational alterations in response to changes in membrane potential, regulating conductance through the intrinsic pore (Ragsdale and Avoli, 1998).

The main structural component of the neuronal Na^+ channel is the α–subunit, which forms the ion-conducting pore and confers voltage dependency (Catterall, 1992). In the mammalian brain, the α- subunit associates with two auxiliary subunits designated β_1 and β_2. The β-subunits are not required for basic Na^+ channel activity, but they modulate the expression and function of individual channels (Ragsdale and Avoli, 1998).

At normal membrane potentials, most Na^+ channels exist in a closed, resting state. Upon depolarization, the channels activates, facilitating ion flux. Thereafter, the Na^+ channel enters an inactivated state, from which it is not readily re-activated. Repolarization of the neuronal membrane rapidly converts the channel back to a resting state, from which it can respond to subsequent depolarization (Catterall, 1992; Ragsdale and Avoli, 1998). Neuronal Na^+ channels can cycle through these functional states within a few milliseconds. This characteristic is essential for sustaining the rapid bursts of action potentials necessary for some normal brain functions, and is implicated in the production of epileptic discharges, The neuronal Na^+ channel represents one of the most important targets for AED action (Upton, 1994; Macdonald and Kelly, 1995; Meldrum, 1996; White, 1999).

Ca^{2+} channels

Voltage-dependent Ca^{2+} channels share key structural elements and sequence homology with their Na^{+} channel counterparts (Barchi, 1998). The α_1- subunit of the Ca^{2+} channel is the homologue of the α- subunit of the Na^{+} channel. It forms the Ca^{2+}-sensitive channel pore and confers voltage dependency (Catterall, 1995). In the mammalian brain, the α_1- subunit heterogeneously associates with other subunits designated β, γ and δ. Voltage-sensitive Ca^{2+} channels can be broadly classified into low or high threshold, according to the membrane potential at which they are activated (Hofmann Biel and Flokerzi, 1994). The low-threshold T-type Ca^{2+} channel is expressed predominantly in thalamocortical relay neurons, where it is believed to be instrumental in the generation of the rhythmic 3-Hz spike-and-wave discharge that is characteristic of generalized absence seizures (Coulter Huguenard and Prinee, 1989). High-threshold Ca^{2+} channels are subclassified by their pharmacological properties into L-, N-, P-, Q-, and R-types (Hofmann, Biel and Flokerzi, 1994; Catterall, 1995; Dolphin, 1995). These channels are distributed throughout the nervous system on dendrites, cell bodies, and nerve terminals. The N-, P-, and Q-type channels, in particular, have been implicated in the control of neurotransmitter release at the synapse (Stefani, Spadoni and Bernardi, 1997).

Interest in Ca^{2+} channels has heightened in recent years, following the identification of subunit-specific genetic mutations that can alter channel structure and/or function and that have been implicated in several human neurological diseases (Ophoff et al., 1998). Several AEDs have been reported to block voltage-sensitive Ca^{2+} channel in a subtype-specific manner, an effect that contribute to their antiepileptic actions (Stefani, Spadoni and Bernadi, 1997).

K^+ channels

Neuronal K^+ channels are large protein complexes that form tetrameric structures, the monomers of which are structurally and genetically related to the α- and α_1-subunits of the Na^+ and Ca^{2+}channel, respectively (Barchi, 1998).The association of four subunits (monomers) in the neuronal membrane is required for the formation of a K^+-sensitive pore and, therefore, channel function. More than 40 distinct K^+ channel subunits have been identified, together with several auxiliary subunits. Given heterologous arrangement, it is possible that countless populations of K^+channels, with individual functions and distributions, are expressed in the mammalian brain (Pongs, 1999).

At the neuronal level, K^+ channels are intimately involved in excitability. They are responsible for the action potential down stroke or, more specifically, repolarization of the plasma membrane in the aftermath of Na^+ channel activation (Pongs, 1999). Direct activation of voltage dependent K^+

channels hyperpolarizes the neuronal membrane and limits action potential firing (Porter and Rogawski, 1992). Accordingly, K^+ channels activators have anticonvulsant effects in some experimental seizure models (Gandolfo et al., 1989; Rostock et al., 1996), whereas K^+ channel blockers precipitate seizures (Yamaguchi and Rogawski, 1992).

Modulation of ion channels by antiepileptic drugs

Phenytoin (PHT)

PHT was discovered following a search to identify a nonsedative analogue of PB (Merritt & Putnam, 1938). It has become a first-line treatment for partial and generalized tonic-clonic seizures (Brodie and Dichter, 1996). PHT is believed to exert its anticonvulsant effect primarily by an action on voltage-dependent Na^+ channels (Tunnicliff, 1996)

PHT has also been reported to block high voltage-activated Ca^{2+} channels (Schumacher, 1995) and, paradoxically, to reduced K^+ currents (Nobile and Vercellino, 1997). There is further unsubstantiated evidence to suggest that PHT potentiates the action of GABA at specific molecular subtypes of the $GABA_A$ receptor (Granger et al., 1995).

Carbamazepine (CBZ)

CBZ is chemically related to the tricyclic antidepressants. First introduced in 1963, it is widely used in the treatment of partial and generalized tonic-clonic seizures (Brodie and French, 2000). CBZ has been reported to stabilize the inactive form of the Na^+ channel in a voltage-frequency-, and time-dependent fashion (Courtney and Etter, 1983). Inhibition of glutamatergic neurotransmission has also been implicated in the mechanism of CBZ action.

Lamotrigine (LTG)

Larmotrigine (LTG) is a new AED that was developed as a result of a once-presumed link between anticonvulsant and anti-folate properties (Reynolds et al., 1966). It has proved to have a broad spectrum of activity, with efficacy for partial, absence, myoclonic, and tonic-clonic seizures (Leach and Brodie, 1995).

Oxcarbazepine (OXC)

Oxcarbazepine (OXC) is relatively novel AED, with widespread geographical approval for clinical use (Tecoma, 1999). It is closely related to CBZ in structure. The keto-substitutions at the 10 and 11 positions of the dibenzazepine nucleus do not affect the therapeutic profile of the drugs when

compared with CBZ, but result in altered biotransformation and better tolerability (White, 1999).

The structural modifications circumvent the 10,11-epoxide metabolite of CBZ that is believed to be responsible for many of its side effects and its ability to induce cytochrome P450-dependent hepatic metabolism (Tecoma, 1999). OXC is essentially a pro-drug, and is rapidly and completely reduced in the liver to its active metabolite, the monohydroxy derivative (10,11-dihydro-10- hydroxy CBZ.

Ethosuximide (ESM)

ESM has been used in treatment of generalized absence seizures for over 30 years (Brodie and Dichter, 1997). It has no consistent efficacy for any other seizure type. ESM exerts its anti-absence effects by reducing T-type Ca^{2+} currents in thalamocortical relay neurons (Coulter Huguenard and Prince, 1989).

Zonisamide (ZNS)

Clinical evidence to date suggests that ZNS is effective against partial and generalized seizures, and has particular efficacy in the progressive myoclonic epilepsies that are often resistant to AED treatment (Dichter and Brodie, 1996; Kyllerman and Ben-Menachem, 1998).

Antiepileptic drugs with multiple mechanisms of action

Sodium valproate (VPA)

The antiepileptic properties of VPA were discovered serendipitously when valproic acid was employed in animal studies as a solvent for drugs under formal investigation (Meunier et al., 1963). VPA has since proved to be an extremely useful AED, with a broad spectrum of activity and particular efficacy in the generalized epilepsies (Brodie and Dichter, 1996).

VPA has been reported to block voltage-dependent Na^+ channels. It reduces sustained repetitive firing of mouse neurons in culture (McLean and Macdonald, 1986). VPA may also block T-type Ca^{2+} channels in a manner similar to that reported for ESM.

There is evidence to suggest that VPA elevates whole brain GABA levels and potentiates GABA responses, possibly by enhancing GAD activity and inhibiting GABA degradation (Loscher, 1999).

Single doses of VPA decrease brain levels of the excitatory amino acid aspartate, without influencing those of glutamate or GABA (Schechter, Trainer and Grove, 1978). Decreases in aspartate concentration have been

shown to correspond with the period of anticonvulsant activity in animal models (Chapman, Meldrum and Mandes, 1983).

Gabapentin (GBP)

GBP is a novel compound, structurally related to GABA, which is effective in the adjunctive treatment of partial seizures, with or without secondary generalization (Dichter and Brodie, 1996). It was originally designed as a GABAmimetic that could freely cross the blood-brain barrier. However, subsequent studies have shown that GBP does not directly interact with GABA receptors (Taylor et al., 1998) or transporters (Su et al., 1995; Macdonald and Greenfield, 1997).

Felbamate (FBM)

FBM was licensed in the United States in 1993 as monotherapy and add-on treatment for partial-onset and primary generalized tonic-clonic seizures in adults and for children with Lennox-Gastaut syndrome (Dichter and Brodie, 1996). Its initial clinical success was tempered by the significant incidence of aplastic anemia and hepatotoxicity revealed in post-marketing surveillance (Pellock and Brodie, 1997).

Topiramate (TPM)

The sulfamate derivative TPM is active against partial-onset and generalized seizures in humans (Wilson and Brodie, 1996; Brodie and French, 2000). TPM has multiple mechanisms of action, including inhibition of Na^{+} and Ca^{2+} currents blockade of the AMPA/kainate subtype of glutamate receptor, and facilitation of GABA effects at the $GABA_A$ receptor.

Antiepileptic drugs with unknown metabolisms of action

Levetiracetam (LEV)

LEV is the S-enantiomer of the ethyl analogue of piracetam, a widely used nootropic agent in the elderly (Loscher and Honack, 1993). As the most recently licensed AED, clinical experience with LEV is limited (Genton and Van Vleymen, 2000). Results of clinical trials suggest that it is effective against partial seizures with or without secondary generalization (Bialer et al., 1999). However, more extensive investigation of LEV is required before its full spectrum of clinical activity is revealed.

LEV appears to have a unique mode of action that, at this time, remains to be clearly characterized. Exhaustive preclinical investigations suggest

that it does not interact directly with any of the traditional targets, including Na^{+}, Ca^{2+}, and K^{+} channels or the GABA and glutamate neurotransmitter systems (Noyer et al., 1995). It is believed to bind to a specific, as yet unidentified, site on the synaptic plasma membrane.