1. Introduction

1.1. Drug design, discovery and development

The discovery of new drug is a challenging, complicated and expensive endeavour. Indeed, to establish exact figures are difficult but recent data indicate that it take around 12 to 15 years and close to 1 billion US$ to develop and bring a new drug to the market. Additionally, according to recent analysis, only 11 out of 100 compounds enters phase I clinical trial and one out of 10 enters phase III clinical trial and has the potential to become marketed drug. Many of these drugs never pay off the money invested in their development. Hence the success rate of drug discovery and development process of new drug may be the key factor for the survival of pharmaceutical and bulk drug industries (Hughes *et al.*, 2011). A current estimate of the cost of drug development is found to be more than 883.6 million US$ (Morgan *et al.*, 2011). An integrated and insightful look at the successful drug system depends upon the ability to identify new chemical entities that have the potential to treat disease in a safe and efficient manner. Although at the end of the nineteenth century, the approaches for discovering a new drug were mostly guided by trial and error methods (Kaul, 1998), but the advent of liquid chromatography based biochemical separation of enzymes and cloning of receptors and ion channels in the 1980s led to a new era in the field of rational drug discovery (Brown and Superti–Furga, 2003). The generation of lead compounds result from screening the library of compounds by utilizing potential targets (enzymes, receptors, ion channel, etc.). The "lead" then undergoes the process of optimization for efficiently modulating a specific biochemical mechanism. The various synthetic strategies used from lead optimization are bioisosteric replacement *via* classical and non–classical methodology, prodrug and analog design etc. Bioisosteric replacements are carried out in designing new drugs to improve pharmacological activity together with increasing the selectivity for a receptor or isoform of an enzyme. It also optimizes the pharmacokinetics parameters (Patani and LaVoie, 1996; Lima and Barreiro, 2005). Prodrug based design is another potential optimization technique, and it is a fact that 10% of the drugs approved worldwide can be classified as prodrugs. The prodrug design technique is applied to improve the physicochemical, biopharmaceutical and pharmacokinetic properties of pharmacologically potent compounds (Zawilska *et al.*, 2013). The analog design of an existing drug molecule allows for the generation of molecules having structural and pharmacological similarities with the original compound (Wermuth, 2006). These kinds

of molecular modifications allow the rational design of prospective lead candidates into safer and clinically efficacious molecules. Thus, the driving forces of modern drug discovery are biological targets, genetic studies, transgenic animal models, molecular biology, gene technology, high throughput screening and protein science (Lounnas *et al.*, 2013). Further, new synthetic methods and technologies are now available to the synthetic and medicinal chemist that allows for the necessary molecular modification (MacCoss and Baillie, 2004).

With the advances in fast computing technology, computer assisted drug design (CADD) also allows for studying the molecular similarity approaches such as comparative molecular similarity indices analysis (CoMSIA), quantitative structure–activity relationships (QSAR) e.g. comparative molecular field analysis (CoMFA), atom–based 3D QSAR and pharmacophore model generations. Broadly, the drug design paradigm can be categorized into two types: structure based drug design (SBDD) and ligand based drug design (LBDD). The goal of modern drug design in context to SBDD is to select a specific target that is involve in the pathophysiology of a particular disease and discover compounds that interact with specific target and bring out a desirable therapeutic outcome (Moon and Howe, 1991). Drug development by SBDD is guided by 3D structure of known targets with defined active sites. The active site within the 3D structure of a target protein is determined either by X–ray crystallography or NMR. Once the ligand bound 3D structure is known, large collections of chemical compounds can be screened virtually (Mandal *et al.*, 2009).

Ligands with potent activity can be found by screening a molecule database with docking software. Frequently used techniques in this approach are docking and molecular dynamics simulation (Chen *et al.*, 2009). Molecular dynamics mimics the actual behaviour of real molecules in motion within a biological system. The receptor motions clearly play an essential role in the binding of most small molecules with the targets. The positions of these atoms are moved according to Newton's laws of motion. Various molecular dynamics simulation software packages are named according to their default force fields are AMBER (Assisted Model Building with Energy Refinement), CHARMM (Chemistry at HARvard Macromolecular Mechanics) and NAMD (NAnoscale Molecular Dynamics) (Durrant and McCammon, 2011).

Alternatively, if the structure of the target protein is not available, the structure of the protein can be predicted by homology modelling. The approach of homology relies on

the sequence of the target protein with at least one known structures. This sequence alignment procedure has become a popular technique to obtain the 3D representation of the target in the absence of crystal structures (Cavasotto and Phatak, 2009). Likewise, if the 3D structure of a protein of a particular target is available without any functional information, computational method such as active site prediction assist to identify which properties of active residues are required for catalysis and/or recognition for a viable ligand–receptor interaction (Ko *et al.*, 2005).

LBDD is another approach used in the absence of the receptor 3D information and is based on knowledge of molecules that bind to the biological target of interest. 3D QSAR and pharmacophore modeling are the most important and widely used tools that provide predictive models suitable for lead identification, optimization (Acharya *et al.*, 2011) and database mining (Das *et al.*, 2011).

The examples (Hoffmann and Metternich, 2012) of various potent molecules with favourable therapeutic application that emerged by the applications of modern drug designing techniques are protease inhibitors such as saquinavir and ritonavir, kinase inhibitors such as imatinib and vemurafenib, proton pump inhibitors (pantoprazole), angiotensin receptor antagonist (saralasin) and ACE inhibitors (captopril), antidiabetic dipeptidyl peptidase–4 inhibitors (sitagliptin). It is reasonable to state that tailor made drug using the tools of drug design and molecular modelling has indeed been very successful in some disease areas. Similarly, several anticonvulsant drugs were also discovered using various drug design approaches exemplified by the discovery of levetiracetam and it analog brivaracetam (Rogawski, 2008). The recent discovery of perampanel an orally active and highly selective, non–competitive AMPA receptor antagonist is an example of focused drug discovery program at Eisai Research Laboratories, Japan (Hibi *et al.*, 2012; Satlin *et al.*, 2013). CADD and modelling are now widely used to study targets relevant to anticonvulsant agents and some of the proteins studies using CADD are voltage gated sodium and potassium channels, NMDA, AMPA and $GABA_A$ receptors (Weaver, 2011).

1.2. Epilepsy: an overview

Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures in patients having two unprovoked seizures greater than 24 hour apart. The definition has been further conceptualized, and epileptic seizure is

defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) now consider epilepsy as a disease (Fisher *et al.*, 2014) of the brain and defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring>24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years.
3. Diagnosis of an epileptic syndrome.

According to the WHO, epilepsy affects around 50 million people worldwide and approximately 80% of epileptic individuals are found in the developing regions. Epilepsy responds to treatment about 70% of the time, nevertheless about three–fourths of the affected people in the developing countries do not get the necessary treatment (http://www.who.int/mediacentre/factsheets/fs999/en/). India accounts for 10–20% (5–10 million) of the global burden of epilepsy (Joshua and Mahapatra, 2013). The incidence of epilepsy in the developed countries is between 40–70/100,000/year and the ratio is much higher (120/100,000/year) in poor countries. It is the most common serious brain disorder worldwide with no age, racial, social class, national or geographic boundaries (http://www.who.int). The economic burden of epilepsy in India per case each year amounted to US $344 and the total cost for the estimated 5 million cases resident in India was equivalent to 0.5% of the gross national product (de Boer *et al.*, 2008).

1.3. Etiology of epilepsy

15–20% of all generalized epilepsies are idiopathic in nature (Jallon and Latour, 2005). About 40% of patients suffering from epilepsy have a genetic background but commonly an imbalance between glutamate and γ–aminobutyric acid (GABA) neurotransmitter systems can lead to hyperexcitability (Engelborghs *et al.*, 2000). Prenatal brain injury including hypoxia–ischemia and infection frequently affect the developing brain of infants, and they are also prone to infliction by epileptic disorder (Robinson, 2005). Another most common cause of secondary epileptic seizures in developing world is due to the formation of cyst in the brain known as neurocysticercosis. It is a condition where the brain is infected by the larvae of the pork

tapeworm *Taenia solium* (Pal *et al.*, 2000; Sil *et al.*, 2012). Studies suggest that the neurocysticercosis probably affects an estimated of 1 million patients in India with active epilepsy (Rajshekhar *et al.*, 2006). Studies also highlight the possibility of the contribution of inflammatory cytokines such as IL–1β, TNF–α and IL–6 in the etiopathogenesis of seizures. These cytokines were found to be overexpressed within the specific areas of the brain responsible for seizure generation and propagation in experimental models (Vezzani *et al.*, 2008). Further, various experimental data suggest that both innate and adaptive immunity may be involved in epilepsy. Autoantibodies directed against brain cells may results in epilepsy (Granata *et al.*, 2011). Traumatic brain injuries may cause epilepsy. It is one of the most common and important causes of acquired epilepsy (Lowenstein, 2009). Glutamate released at the synapse acts on post–synaptic ionotropic and metabotropic receptors. In certain pathological condition, an increase in glutamate release has been observed (Chapman, 2000) and hyper–activation of glutamate receptors on neurons and astrocytes appears to play a pivotal role in the initiation and spread of seizure activity (Dingledine, 2012).

1.4. Classification of epilepsy

A systematic classification of epilepsy is important for better implementation and choosing of treatment strategies. In the year 1981, the first international classification of seizure types was officially updated and came into existence based on clinical observations by the International League Against Epilepsy (ILAE). There are three main types of seizures: partial, generalized, and unclassified epileptic seizure. A general and well–known classification of epilepsy (Goldenberg, 2010; Das *et al.*, 2012) is as follows:

1. Partial (focal) seizures: They are of three types.
    - Simple partial seizures (with motor, sensory, autonomic, or psychic signs; consciousness is not impaired).
    - Complex partial seizures (consciousness is impaired).
    - Partial seizures evolving to secondarily generalized seizures.
2. Primarily generalized seizures classified as
    - Absence (petit mal) seizures
    - Myoclonic seizures
    - Clonic seizures

- Tonic seizures
- Tonic–clonic (grand mal) seizures
- Atonic seizures

3. Unclassified seizures are
    - Neonatal seizures
    - Infantile spasms

The previous classification proposed by the ILAE has been revised with new terminology and concept based on the mode of seizure onset. The generalized epileptic seizures are conceptualized as originating at some point that include cortical and subcortical structures of the brain and may include the entire region of the cortex. Alternatively, focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere of the brain.

The specific changes that have been made to the 1981 classification (Berg *et al.*, 2010) of seizures are as follows:

1. Neonatal seizures are no longer considered as a separate entity.
2. Simplification and alteration of previous sub–classification of absence seizures. Myoclonic absence seizures and eyelid myoclonia are now recognized.
3. Spasms were not clearly acknowledged in the 1981 classification of seizures. The term ‘‘epileptic spasms” has been included. Moreover, as knowledge on this particular disorder is limited; therefore, it has been placed in a separate group as unknown.
4. Elimination of the dissimilarity between the different types for focal seizures, (e.g., complex partial and simple partial).
5. Myoclonic atonic seizures are now recognized.

1.5. Management of epilepsy

1.5.1. Drug therapy

The management of seizures in patient with epilepsy depends largely on the rational use of anticonvulsant drugs. Majority of the drugs used in the treatment of epilepsy are believed to either suppress excitatory or accentuate inhibitory neurotransmission. The broad varieties of available drugs are not target specific and they exert their action on multiple biological targets (White *et al.*, 2007). There is no evidence that drugs used against epilepsy provide a complete cure or alter the natural course of the disorder.

However, the anticonvulsant drug therapy may be withdrawn from certain patients after successful control of seizure for successive two or more years (Bromfield *et al.*, 2006b). Majority of the drugs used in the treatment of epilepsy are associated with adverse effects and affect up to 40% of the patients and leading to treatment failure. The choice of a particular drug or combination therapy is determined by the adverse effect profile of the drugs (Perucca and Meador, 2005). Nearly all the first–generation anticonvulsant drugs, particularly carbamazepine, phenytoin, primidone, and benzodiazepines, are associated with substantial risk of coordination difficulties. These disturbances (unsteadiness, imbalance, or ataxia) were also observed in a meta–analysis of randomised, placebo–controlled, adjunctive treatment trials with gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide when compared with placebo (Perucca and Gilliam, 2012). Another commonly encountered adverse effect associated with several anticonvulsant drugs is hepatotoxicity or more commonly known as drug induced liver injury (Björnsson, 2008). A generalized hypersensitivity reaction along with drug induced liver injury is involved with lamotrigine, carbamazepine, phenobarbital and phenytoin (Ahmed and Siddiqi, 2006).

Despite the adverse effects, drug therapy is the first line of treatment initiated in epilepsy. The primary goal of drug therapy is maximizing seizure control while minimizing adverse drug effects and devoid of any alteration with the normal brain function. The drugs utilized commonly for the treatment of epilepsy along with their mechanism of action are listed in Table 1.1.

Table 1.1. Anticonvulsant drugs and their mechanism of action

Drugs	Mechanism of action	References
Phenytoin	Voltage–dependent blockade of membrane sodium channels	Yaari *et al.*, 1986
Carbamazepine	Inhibits voltage–gated sodium channels	Ambrósio *et al.*, 2002
Clonazepam	Binds to $GABA_A$ receptors and potentiate GABAergic inhibition	Riss *et al.*, 2008
Ethosuximide	Reduces calcium currents *via* T–type calcium channels	Czapiński *et al.*, 2005
Gabapentin	Selectively acts on voltage gated calcium channels and exert inhibitory effects	Sills, 2006
Lacosamide	First selectively enhances slow inactivation of voltage–gated sodium channels Secondly, lacosamide binds to collapsin response mediator protein 2	Perucca *et al.*, 2008
Lamotrigine	Blocks neuronal α4β2 nicotinic acetylcholine receptors	Zheng *et al.*, 2010
Tiagabine	Inhibits GABA reuptake selectively in presynaptic neurons and glial cells and increases the availability of GABA at the synapse	Landmark, 2007
Sodium valproate	Increases GABA levels probably by increasing succinic semialdehyde which inhibits GABA transaminase thereby increasing the GABA level.	Johannessen, 2000
Retigabine	Interact with the KCNQ2/KCNQ3 subunits of the potassium channels; $GABA_A$ receptors and it also weakly block the sodium and calcium channels	Harris and Murphy, 2011
Levetiracetam	Binds selectively to synaptic vesicle and modulate synaptic vesicle exocytosis and neurotransmitter release	Pitkänen, 2005
Pregabalin	Selectively acts on voltage gated calcium channels and exert inhibitory effects	Sills, 2006
Topiramate	Selectively blocks excitatory synaptic transmission mediated by GluR5 kainate receptors	Gryder and Rogawski, 2003
Vigabatrin	It irreversibly inhibits GABA transaminase, the enzyme responsible for the breakdown of GABA	Willmore *et al.*, 2009
Zonisamide	Blocks voltage–sensitive sodium channels and reduces voltage–sensitive T–type calcium currents without affecting L–type calcium currents.	Leppik, 2004

1.5.1.1. Various targets of anticonvulsant drugs

A brief outline of some important targets of anticonvulsant drugs are summarized in the following respective headings:

1.5.1.1.1. Voltage–gated sodium channels

Voltage–gated sodium channels (VGSCs) play an essential role in the initiation and propagation of action potentials in neurons. The VGSCs of the mammalian brain composed of a complex of nine α subunits ($Na_v1.1$–$Na_v1.9$) along with one or more auxiliary β subunit (Yu and Catterall, 2003). There are three main conformational states of voltage–gated channels i) a closed (resting potential), ii) an open (membrane depolarization), and iii) an inactivated state (sustained depolarization) (Lerche *et al.*, 2001). The drugs viz. phenytoin and carbamazepine acts *via* VGSCs and prolongs the inactivated state of the channels and block the neuronal firing (Köhling, 2002).

1.5.1.1.2. Voltage–gated calcium channels

Voltage–gated calcium channels (VGCCs) are integral membrane proteins that form calcium selective pores (α1 subunit) in the plasma membrane. The principle component of VGCCs consists of α1, α2, β and δ subunit. VGCCs control the neuronal excitability by facilitating calcium influx. Activation of low–voltage–activated (T–type) calcium channels induce burst–firing in the thalamocortical circuitry and give rise to spike wave discharges (Cain and Snutch, 2011). Entry of Ca^{2+} ions through T–channels causes depolarization of the membrane and leads to the generation of low threshold spikes and activates eruption of Na–dependent action potentials (Zamponi *et al.*, 2010). The drugs ethosuximide acts *via* blockade of T–type calcium channels (Gomora *et al.*, 2001).

1.5.1.1.3. Voltage–gated potassium channels (K_V channels)

K_v channels are transmembrane channels specific for potassium. When an action potential is generated, the function of K_v channels is to return the depolarized cell to a resting state (repolarize) with an influx of potassium (Hu *et al.*, 2014). Therefore, activation of potassium channels in excitable cells reduces the excitability. In excitable cells such as neurons, K_v channels are expressed together with the voltage–gated sodium and/or calcium channels. Retigabine is the drug that cause profound hyperpolarizing shift in the voltage–dependence of channel activation (Wulff *et al.*, 2009). It is an

allosteric modulator of KCNQ2–5 ion channels and is the first neuronal potassium channel opener for the treatment of epilepsy (Gunthorpe *et al.*, 2012).

1.5.1.1.4. Inhibitory neurotransmission

According to the GABA philosophy, the convulsion arises due to imbalance of two principle neurotransmitter in the brain, L–glutamic acid, an excitatory neurotransmitter and γ–aminobutyric acid (GABA), an inhibitory neurotransmitter. The concentration of GABA is regulated by two PLP (pyridoxal 5´ phosphate) dependent enzymes, L–glutamic acid decarboxylase (GAD), which converts glutamate to GABA and GABA aminotransferase (GABA-AT) that degrades GABA to succinic semialdehyde. Succinic semialdehyde is toxic to the cells and there is no build–up of this metabolite owing to immediate oxidation of the compound into succinic acid by succinic semialdehyde dehydrogenase (SSADH). GABA is formed within the GABAergic axon terminals by transamination of α–ketoglutarate to glutamic acid, which is then decarboxylated by glutamic acid decarboxylase (GAD) to GABA (Figure 1.1.) (Treiman, 2001).

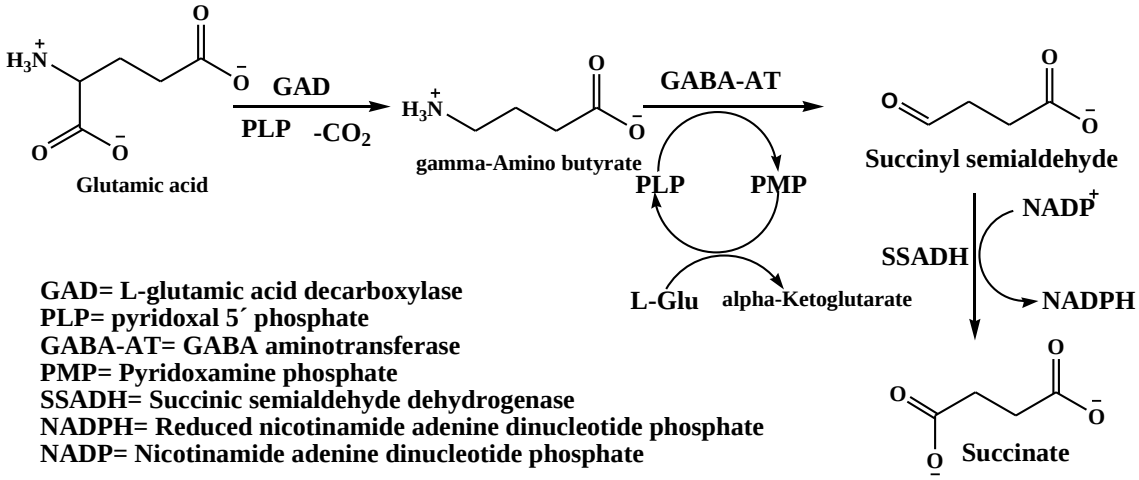

Figure 1.1. GABA biosynthesis.

GABA is one of the principle inhibitory neurotransmitters in the brain and interacts with three types of receptors viz. $GABA_A$, $GABA_B$ and $GABA_C$. Antiepileptic drugs under benzodiazepine class binds to $GABA_A$ receptors and facilitate the opening of the chloride channel as the latter exist as complex with $GABA_A$. It causes chloride anions to enter the neuron, which gets hyperpolarized (Czapiński *et al.*, 2005) and suppress epilepsy. Alternatively, sodium valproate increases the GABA levels probably by increasing succinic semialdehyde which inhibits GABA transaminase thereby increasing the level of GABA (Johannessen, 2000). Tiagabine is another category of drug that

blocks neuronal and glial uptake of GABA by inhibiting the GABA uptake transporter, GAT1 and increase the synaptic GABA levels and inhibits seizures (Czuczwar and Patsalos, 2001).

1.5.1.1.5. Excitatory neurotransmission

The amino acid glutamate is the major excitatory neurotransmitter in the brain. There are several subtypes of glutamate receptors and can be broadly classified as ionotropic and metabotropic glutamate receptor. The ionotropic are further classified as the α–amino–3–hydroxy–5–methyl–4–isoxazolepropionic acid (AMPA), kainate and *N*–methyl–D–aspartate (NMDA) receptors. The NMDA receptor family is composed of seven subunits, NR1, NR2A–D and NR3A and B while AMPA receptors are composed of a four–subunit family (GluR1–4). Kainate receptors are composed of two related subunit families, GluR5–7 and KA–1 and 2 (Kew and Kemp, 2005). All the ionotropic glutamate receptors are permeable to Na^+ and K^+, and influx of Na^+ and outflow of K^+ through these channels contribute to membrane depolarization and generation of the action potential. The other major type of glutamate receptor is the metabotropic receptor. It functions *via* receptor–activated signal transduction involving membrane–associated G–proteins potential (Bromfield *et al.*, 2006a; De Sarro *et al.*, 2005). Among them, the AMPA receptor received considerable interest in the field of anticonvulsant drug research and their role in the events of epileptogenesis has been thoroughly studied (Jensen *et al.*, 2007).

The focus on recent research on antiepileptic drugs is based on the ability of the drugs to block AMPA receptors (Figure 1.2.) either competitively or non–competitively. Majority of the potential anticonvulsant developed till dates are non–competitive antagonists (Chimirri *et al.*, 1999; Rogawski, 2011) because of the following reason:

- Non–competitive antagonists are preferred because, in the presence of high glutamate concentration, the competitive antagonist gets displaced from the agonist binding site.
- Non–competitive antagonists can remain effective independently of the level of glutamate.
- They do not influence the normal glutamatergic activity even after prolonged use.

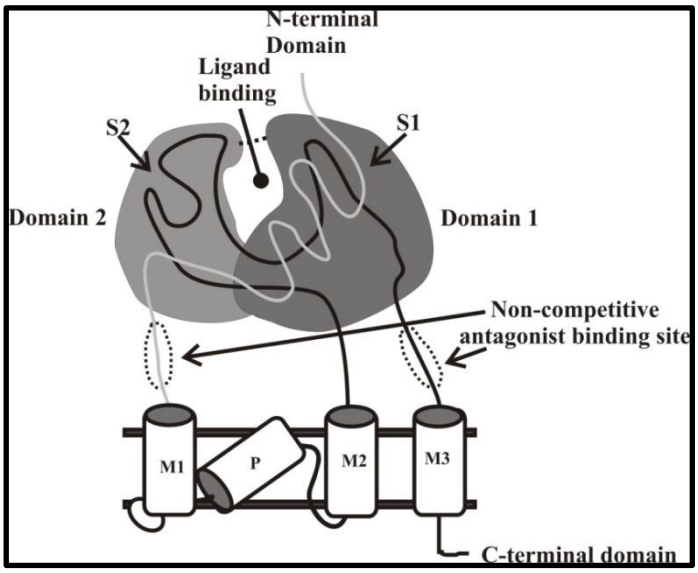

Figure 1.2. Schematic model of an AMPA receptor subunit. The putative sites of action of allosteric non–competitive antagonist talampanel are also shown. The ligand binding core consists of two domains (S1 and S1) attached by linkers to the cation–channel domain consisting of three membrane–spanning segments (M1–3) and a pore loop (P). The C terminal domain is located intracellular (Bialer *et al.*, 2007) (Printable licence from Elsevier; Lic. No. 3401960077755).

The prototype non–competitive AMPA receptor antagonist is a 2, 3–benzodiazepine derivative (GYKI 52466) (Donevan and Rogawski, 1993) provide opportunities for the development of talampanel (Gitto *et al.*, 2003) and structurally diverse compound such as perampanel having a 2, 3'–bipyridin–6'–one nucleus (Rogawski and Hanada, 2013). The drug inhibits AMPA–induced increases in intracellular Ca^{2+} and selectively blocks AMPA receptor–mediated synaptic transmission, thus reducing neuronal excitation (Shih *et al.*, 2013).

1.5.1.1.6. Enzymes

GABA Transaminase

GABA transaminase is the enzyme responsible for the catabolism of GABA. Vigabatrin (γ–vinyl GABA) is an irreversible GABA transaminase inhibitor that has been designed with the goal to increase the synaptic GABA concentrations and inhibiting seizure activity (Willmore *et al.*, 2009).

Carbonic anhydrase

Carbonic anhydrase is a zinc containing enzyme that catalyzes the reversible hydration of carbon dioxide to bicarbonate and proton (Lindskog, 1997). The enzyme is the target

for various drugs, such as acetazolamide that is used for the treatment of glaucoma and epilepsy. The exact mechanism is not known; however, it is thought that reduced brain carbonic anhydrase causes accumulation of CO_2 in the extracellular space. This stabilizes the membrane excitability and limits the seizure spread especially in generalized tonic clonic seizure (Stafstrom, 2009).

1.5.1.1.7. SV2A

The synaptic vesicle proteins (SV2s) are twelve transmembrane glycoproteins and in particular the SV2A is considered as a novel target for the anticonvulsant drug levetiracetam (Lynch *et al.*, 2004). Although, the exact mechanism *via* which levetiracetam acts is not known, however, it is thought that the drug binds SV2A and inhibits voltage dependent presynaptic calcium channels thereby reduces neuronal excitability (vogl *et al.*, 2012).

1.5.2. Other treatment strategies (Non–pharmacological interventions)

1.5.2.1. Ketogenic diet therapy

In the year 1920, ketogenic diet was adopted in view of the observation that fasting had antiseizure properties. With the development and emergence of the number of anticonvulsant drugs, the physicians lost their interest in a ketogenic diet. In recent years, the use of ketogenic diet has again resurfaced, particularly for the treatment of refractory epilepsy. The diet includes very high in fat and low in carbohydrates. The mechanism underlying the use of the diet is that it simulates starvation and stimulates the production of acetoacetate, β–hydroxybutyrate, and acetone (ketone bodies) (Barañano and Hartman, 2008). The ketone bodies are thought to not only inhibit neuronal hyperexcitability but also induce a protective effect against refractory seizure (Kim do and Rho, 2008). Several other mechanistic theories have been proposed, and these include modification of the tricarboxylic acid cycle to increase GABA synthesis in the brain, limit reactive oxygen species generation, and increase energy production in the brain tissue. This results in hyperpolarization of neurons thereby stabilizing synaptic function and increasing resistance to seizures throughout the brain (Rogovik and Goldman, 2010). Recent studies suggest that the ketogenic diet in children results in seizure control in certain cases and the effects of which are comparable to modern

antiepileptic drugs. However, gastrointestinal side effects overshadow the therapy (Levy *et al.*, 2012).

1.5.2.2. Surgical treatment of epilepsy

Surgery of brain in epilepsy is carried out during the failure of drug therapy or when the localization of the origin of the seizures to a particular site in the brain is achieved. Recent studies revealed that surgical treatment is superior to continued medical treatment with two anticonvulsant drugs or if the seizure is focal in nature (Schulze–Bonhage and Zentner, 2014). Modern techniques like functional neuroimaging, neurosurgery, and neuroanaesthesia have tremendously improved the surgical option for children with intractable epilepsy. A better quality of life (QOL) is achieved by an early surgery and allows the child to lead a normal life. Significantly more patients in the surgical group achieved meaningful improvement in epilepsy specific measures of QOL at 6 and 12 months post–surgery compared to drug treated group (Jayalakshmi *et al.*, 2014; Fiest *et al.*, 2014).

1.5.2.3. Vagal nerve stimulation

In 1997, the vagus nerve stimulation (VNS) was approved by the US FDA as an adjunctive treatment for refractory epilepsy. This particular treatment strategy is reserved for those patients who are either poor candidate for surgery or in whom the latter option has failed. The stimulation procedure is reserved for adults and adolescents with partial epilepsy (Englot *et al.*, 2011). Nevertheless the therapy is a viable treatment option for patients with drug–resistant idiopathic generalized epilepsy (Kostov *et al.*, 2007). The mechanism underlying the therapeutic benefits in the form of suppression of seizure by stimulation of the vagus occurs through activation of the serotonin–containing neurons in the raphe nuclei (Krahl and Clark, 2012).