Brain Neurotransmitters (NTs)

Satisfaction of the experimental criteria for identification of synaptic transmitters can lead to the conclusion that a substance contained in a neuron is secreted by that neuron to transmit information to its post synaptic target (Bloom, 1996). The earliest transmitters considered for central roles were acetylcholine and norepinephrine (NE). largely because of their established roles in the somatic motor and autonomic nervous systems. In the 1960s, serotonin (5-Hydroxy- Tryptamine or 5-HT), epinephrine and dopamine (DA) were investigated as potential CNS transmitters. In the early 1970s the availability of selective and potent antagonists of gamma amino butyric acid (GABA), glycine and glutamate, all known to be enriched in brain, led to their acceptance as transmitter substances in general (Curtis et al, 1971; Otsuka, 1973). The compounds now to be considered-catecholamines (DA, NE, and epinephrine), serotonin, histamine (HA) and GABA-can be grouped together not only chemically, as cerebral amines associated with neurotransmission, but also cytologically, because of their occurrence in distinctive cell types and pathways in the brain. With catecholamines and serotonin, the cells concerned have their cell-bodies largely in the brain stem, from where they send highly ramifying processes which can affect a large part of the brain including the neocortex (Ganong, 1991).

After the discovery of 5-HT in blood in 1948 during a routine survey of its distribution within the body, it was found in the brain; prior to this there had been no reason to suspect its presence there (Brodie and Shore, 1957; Page and Carlsson,
Since that time, studies of 5-HT have had a pivotal role in advancing our understanding of the neuropharmacology of the central nervous system (CNS).

Most of the brain 5-HT is localized in the thalamus, hypothalamus, midbrain and raphe nuclei of the lower brain stem (Page and Carlsson, 1970). NE has a patchy distribution in the central nervous system. The cell bodies of the NE containing neurons are located in the locus coeruleus (LC) and other nuclei in the pons and medulla. NE is most concentrated in the hypothalamus and in certain zones of the limbic system such as the central nucleus of the amygdala and the dentate gyrus of the hippocampus (Ganong, 1991). However, this catecholamine also is present in significant, although lower amounts in most brain regions. Detailed mapping studies indicate that most noradrenergic neurons arise either in the LC of the pons or in neurons of the lateral tegmental portion of the reticular formation. From these neurons, multiple branched axons innervate specific target cells in a large number of cortical, subcortical, and spinomedullary fields (Foote et al, 1983). Although originally regarded only as a precursor of NE, assays of distinct regions of the CNS eventually revealed that the distribution of DA and NE are markedly different. In fact, more than half the CNS content of the catecholamine is DA and extremely high amounts are found in the basal ganglia (especially the caudate nucleus), the nucleus accumbens, and the olfactory tubercle, the central nucleus of the amygdala, the median eminence, and restricted fields of the frontal cortex. For many years, HA which is active in the periphery have been known to produce significant effects on animal behaviour. Relatively recently, however, evidence has accumulated to suggest that HA also might be a central neurotransmitter. Most of the histaminergic neurons are confined to the ventral posterior hypothalamic area, where they are comprised of scattered groups of neurons referred to as the tuberomammillary nucleus (Panula et al, 2000); they give rise to long ascending and
descending tracts to the entire CNS that are typical of the patterns characteristic of other aminergic systems. Based on the presumptive central effects of histamine antagonists, the histaminergic system is thought to function in the regulation of arousal, body temperature and vascular dynamics (Bloom, 1996).

Epilepsy or the occurrence of spontaneous recurrent epileptiform discharges (SREDs, seizures) is one of the most common neurological conditions. There is no single causal factor of the disease. However attempts have been made to identify such factors.

**History of Epilepsy**

The temptation when looking at the history of epilepsy and its treatment is to write off human reactions to epilepsy as a bad joke. One recent writer on epilepsy, Henry Alden Bunker, went straight to the point when he said that ‘the history of epilepsy might well be said as a monument to human error.’ It is easy to see why this is so. Epilepsy is horrifying. The public at large and the doctors in particular are frightened of epilepsy as something beyond their control. There is one pervading theme evident throughout the long, ghastly history of epilepsy and its treatment: the feeling that epilepsy shows the human body in power of a force greater than itself.

**Social History**

Epilepsy is the oldest known medical condition with a history of misunderstanding, misinterpretation and confusion. It was first documented at the time of the Babylonians, 2000 BC. They described attacks that today could be classified as epileptiform. However they attributed each seizure type to being possessed by a different evil spirit or god. The Babylonians had laws that stated that these people could
not marry and could not appear in court. In 400 BC, Hypocrites taught of a condition that he named from the Greek word *epilepsia*, meaning to seize or attack. He described this as having a physical rather than a spiritual cause, and often not as being possessed by the devil. From these times until the twentieth century, the beliefs alternated between seeing this as a medical or a spiritual problem.

**Medical History**

This is no less chequered than the social history. The diagnosis of this condition has always been problematic. Even in this age of advanced technology, the most important diagnostic tool still remains the ability to listen to and interpret information supplied by the patient and any witnesses of the episodes being experienced. Diagnosis therefore remains reliant on the clinical expertise and understanding of the health care professionals. In 1857, potassium bromide was first used to treat seizures. This was not because of any understanding of its now recognized anticonvulsant properties, but because it induced temporary impotence. It was believed at that time that an increased sexual drive caused seizures.

In the early nineteenth century, epilepsy was first identified as a symptom of some underlying cause. Hughling Jackson first described an episode, experienced by his wife, of repetitive uncontrolled movements of one limb. This type of seizure became known as Jacksonian epilepsy. This remained a recognized type of epilepsy until the reclassification of seizures by the International League against Epilepsy in 1982, and these seizures are now known as focal motor seizures. Progress in the understanding and treatment of epilepsy is still trudging at a very sluggish pace.
Epidemiology

Incidence and prevalence studies of epilepsy have been reported from many countries but comparisons are often difficult because investigators have adopted different definitions of epilepsy, classification schemes, and selection bias (Shorvon, 1990). Nevertheless, most studies have found incidence rates of 20-70 cases per 100,000 per year (range 11-134 cases per 100,000 per year) and point prevalence rates of 0.4 to 0.8% (Chadwick, 1990).

Incidence varies with age. The incidence rate is highest in children under 2 years of age and in persons over 65 years of age. About 30% of patients with seizures have an identifiable neurological disorder and the remainder has either idiopathic epilepsy (Elwes et al, 1985). Males are more likely to have a new diagnosis of epilepsy than females. The seizure type and the cause of the seizure changes with age.

Prognostic factors

Since epilepsy is not a homogeneous entity, various factors influence prognosis. Patients with a good prognosis are those with seizures precipitated by alcohol, drugs, or metabolic disturbance; benign syndromes (e.g., benign rolandic epilepsy); generalized seizures; or adult-onset idiopathic seizures (Shorvon, 1984). Patients with the poorest prognosis are those with evidence of diffuse cerebral disorder (often with intellectual or behavior disturbance); early onset seizures; partial or mixed seizure types; progressive neurological disorders; or severe epileptic syndromes (e.g., Lennox Gastaut syndrome, West syndrome). The length of active epilepsy is also important—the longer the seizures continue after the onset of treatment the worse the ultimate prognosis (Elwes et al, 1984).
Genetics

An assessment of the genetic contribution to epilepsy is complicated by the heterogeneity of the condition and by the many possible genetic influences. Epilepsy frequently occurs in families. The parents, siblings, and offspring of a person with epilepsy are more likely than the general population to have epilepsy. This familial aggregation does not necessarily imply a genetic mechanism. In addition to genes, families share environmental exposures that may also increase the risk of epilepsy. Primary generalized epilepsies have a strong genetic contribution (Anderson et al., 1982; Meierkord, 1989).

Pathophysiology

Seizure activity is characterized by paroxysmal discharges occurring synchronously in a large population of cortical neurons. This is characterized on the EEG as a sharp wave or spike. The physiology of a seizure is traceable to an unstable cell membrane or its surrounding, supportive cells (Meldrum, 1990). An abnormality of potassium conductance, a defect in the voltage-sensitive calcium channels, or a deficiency in the membrane ATPases linked to ion transport may result in neuronal membrane instability and a seizure (Benardo and Pedley, 1984). Neurotransmitters (e.g., acetylcholine, norepinephrine, histamine (HA) and corticotrophin-releasing factor) enhance the excitability and propagation of neuronal activity, whereas GABA and dopamine inhibit neuronal activity and propagation. Normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, calcium, and amino acids. Systemic pH is also a factor in precipitating seizures. There may be primary defects in the GABAergic inhibitory system or in the sensitivity or arrangement.
of the receptors involved in excitatory neurotransmission that result in a seizure (Benardo and Pedley, 1984).

**A) Primary non-specific pathological changes with secondary epilepsy**

Epilepsy occurs in association with many underlying abnormalities, including developmental defects; vascular lesions; venous thromboses and subdural hematoma; primary or secondary neoplasm; traumatic lesions; microbial or viral infections; parasitic disorders such as toxoplasmosis, cerebral malaria, and cysticercosis; and degenerative disorders, ranging from lesions induced by perinatal asphyxia to Huntington's chorea. These conditions do not necessarily cause epilepsy and may be only coincidentally present.

**B) Seizures with secondary pathological changes**

Status epilepticus may be followed by acute degenerative changes affecting neurons in the hippocampus and the cortex. Hippocampal or temporal lobe sclerosis is a common necropsy finding in institutionalized patients with epilepsy and is the most frequent abnormality when the anterior temporal lobe is removed during the surgical treatment of intractable seizures. In patients with intractable seizures there is often a history of febrile convulsions in early childhood (Dam, 1980). If such convulsions are prolonged (> 30 min) they are presumed to be the cause of the hippocampal lesion. The extent to which recurrent or prolonged limbic seizures in later life contribute to cell loss in the hippocampus is hard to evaluate. In one study seizures appeared to accelerate the loss that occurs with aging (Hardiman et al 1988).
C) Cellular changes contributing to epileptogenesis

Dendritic degeneration is a non-specific finding, but may be associated with membrane changes, including receptor hypersensitivity, that could contribute to epileptogenesis. Another common finding associated with both generalized seizures and complex partial seizures is an abnormality of cortical maturation often called microdysgenesis. This may be manifest as clusters of abnormally large neurons in the cortex, or as dystrophic groups of neurons in the sub cortical white matter. It has been proposed that such abnormalities predispose to diverse types of epilepsy including primary generalized epilepsy, West’s syndrome, and temporal lobe epilepsy (Ellenberg, 1986). However, their relevance remains uncertain.

Aetiology and precipitation of seizures

Anything that disrupts the normal homeostasis of neuronal cell and disturbs its stability may trigger seizures. The most clearly established of these factors are severe head trauma, infections of the central nervous system (CNS), and stroke, although many other factors are also important antecedents. A hereditary predisposition to seizures has been suggested. Patients with mental retardation and cerebral palsy are at increased risk for seizures. The more profound the degree of mental retardation as measured by IQ, the greater the incidence of epilepsy (Sundaram, 1989). The causes of seizures in the elderly are cerebrovascular disease, tumor, head trauma, metabolic disorder, and CNS infections (Scheuer and Pedley, 1990). Hyperventilation may precipitate absence seizures. Sleep, sleep deprivation, sensory stimuli and emotional stress may initiate seizures. Hormonal changes occurring around the time of menses, puberty, or pregnancy have been associated with the onset of, or an increase in, seizure activity. Other precipitating factors include fever, lack of food, and drugs. A careful
history for theophylline, alcohol, phenothiazines, antidepressants (especially maprotiline), and street drug use should be obtained. Also, antiepileptic drugs (AEDs) in excessive concentrations may cause seizures. Table 2.1 summarizes the common causes of seizures.

Table 2.1: Common causes of seizures (Maheswari, 1993)

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Metabolic disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Head trauma</td>
<td>• Electrolytes</td>
</tr>
<tr>
<td>• Birth injury</td>
<td>• Water</td>
</tr>
<tr>
<td>• Neoplasm</td>
<td>• Glucose</td>
</tr>
<tr>
<td>• Vascular abnormalities</td>
<td>• Amino acids</td>
</tr>
<tr>
<td></td>
<td>• Lipids</td>
</tr>
<tr>
<td></td>
<td>• pH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sudden withdrawal of CNS Drugs</th>
<th>Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alcohol</td>
<td>• Fever</td>
</tr>
<tr>
<td>• Street drugs</td>
<td>• Infection</td>
</tr>
<tr>
<td>• Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>• Antidepressants</td>
<td></td>
</tr>
<tr>
<td>• Antiepileptic drugs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heredity</th>
<th>Idiopathic</th>
</tr>
</thead>
</table>

Classification

The International League Against Epilepsy has developed a classification system (Table 2.2) that combines clinical description with EEG findings. Over 90% of seizure patients may be classified using this system. Using the international classification scheme, seizures may be divided into partial, generalized, or unclassified.
Table 2.2: **Classification of epileptic seizures** (Chadwick *et al.*, 1989)

<table>
<thead>
<tr>
<th>Traditional classification</th>
<th>New nomenclature</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal motor; Jancksonian seizure</td>
<td><strong>I. Partial seizures</strong> (seizures begin locally)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Simple (without impairment of consciousness)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ With motor symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ With special sensory or somatosensory symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ With autonomic symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ With psychic symptoms</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe or psychomotor seizures</td>
<td>2) Complex (with impairment of consciousness)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ Simple partial onset followed by impairment of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>consciousness - with or without automatisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ Impaired consciousness at onset - with or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>without automatisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Secondarily generalized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(partial onset evolving to generalized tonic-clonic seizures)</td>
<td></td>
</tr>
<tr>
<td>Petit mal</td>
<td><strong>II. Generalized seizures</strong> (bilaterally symmetrical and without local onset)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Absence</td>
<td></td>
</tr>
<tr>
<td>Minor motor</td>
<td>2) Myoclonic</td>
<td></td>
</tr>
<tr>
<td>Limited grand mal</td>
<td>3) Clonic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4) Tonic</td>
<td></td>
</tr>
<tr>
<td>Grand mal</td>
<td>5) Tonic-clonic</td>
<td></td>
</tr>
<tr>
<td>Drop attacks</td>
<td>6) Atonic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7) Infantile spasms</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>III. Unclassified seizures</strong></td>
<td></td>
</tr>
<tr>
<td>IV. Status Epilepticus</td>
<td>(prolonged partial or generalized seizures without recovery between attacks)</td>
<td></td>
</tr>
</tbody>
</table>
**Epileptogenesis**

Epileptogenesis is the process responsible for the transformation of normal neuronal populations into neurons that display neurophysiological behaviours associated with epilepsy. To be precise the process of inducing spontaneous recurrent epileptiform discharges (SREDs, seizures) or symptomatic epilepsy in previously normal neuronal networks is called epileptogenesis. (Delorenzo et al, 1998; Severn and Emma, 2000).

**Investigative models of epileptogenesis**

A coordinated experimental design is pivotal for the understanding of epileptic networks. Studies on animal models of epilepsy have contributed greatly in understanding the etiology and etiopathogenesis of the disorder. There are many advantages of using animal model in research work on epilepsy as the etiology, pathogenesis of the disorder and its complications can be clearly understood. There are more than 100 in vivo and in vitro seizure models currently available for epilepsy research (Löschner, 1997; Fariello, 1995). For partial seizure production focal lesions in the brain in the experimental animals can be produced by any physical, chemical or electric stimulation (Maheswari, 1993). All experimental models are not identical to epilepsy. Several animal models for epileptogenesis exist, but not all of them accurately reflect the process in humans. Quite a handful of laboratory models simulate human epilepsy as well as provide a system for studying epileptogenesis (Temkin, 2001; Temkin et al, 2001). Majority of the models’ purpose is to make specific aspects of epilepsy accessible to the kinds of technique needed to answer the questions posed.
Experimental models of epilepsies can be divided into three broad categories: acute, chronic and genetic. Acute models typically use convulsant drugs or changes in extracellular ion concentrations; the epileptogenic activity usually ceases on returning to control conditions. Acute experimental foci are typically made by applying convulsant drugs to normal brain. In humans with focal epilepsy however, and in the alumina gel chronic focus in primates (the experiment preparation which most clearly resembles the human situation), neuropathological studies demonstrate neuronal dropout, gliosis and distortions in neuronal morphology including loss of dendritic spines, simplification of dendritic arborization patterns and shrinkage of the entire neurons (Benardo and Pedley, 1985).

Chronic models typically involve implanted heavy metal compounds, injected toxins, local lesions, repeated stimulation and also some drug applications. These treatments lead to a prolonged state of increased seizure susceptibility, or to recurrent spontaneous seizures. A permanent change of this kind is clearly chronic.

Genetic models depend on identifying epilepsy-prone states in natural populations (e.g. photogenic baboon) or artificial selection for epileptic traits in laboratory species (e.g. tottering mouse, genetically epilepsy-prone rat).

Most definitions of epilepsy specifically exclude the single seizure, so it could be argued that acute models can only assess specific symptoms, interictal spikes or seizures, rather than epileptic states. Chronic models where epileptic discharges recur can be said to resemble more closely epilepsy as a condition. Some of the first experimental models happened to be chronic, e.g. with intracerebral tetanus toxins (Roux and Borrel, 1898) or local freezing (Opencowski, 1883). However it was
studies of the actions of acute (when singly applied) convulsants, such as penicillin, that were responsible for most of the remarkable progress made on the cellular mechanisms of the synchronization of epileptic discharges (Jefferys, 1993).

Both in vitro and in vivo models are important in the study of the development and expression of focal seizures as well as in the preclinical evaluation of antiepileptic treatment (De Deyn and D’Hooge, 1999).

A recent in vitro study using a rat brain slice model demonstrated that epileptogenesis can be attenuated with the early application of valproic acid. The authors of this report induced epileptiform activity in brain slices by removing the most superficial 450-500μm of neocortex (Yang and Benardo, 2000). This is not a common model for the study of epileptogenesis, but its findings are provocative and suggest a potential role for early anticonvulsant treatment of brain injured patients. Over the last few years, several laboratories have started to use brain slices prepared from animals made epileptic with one of the chronic or subacute treatments, which provides the prospect of getting the best of both worlds, albeit with the added problem of distinguishing the initial causes of the epileptic activity from its long-term consequences. Although many attribute a potential usefulness of the different slice models in the study of epileptogenesis, the mainstay of investigative models involves in vivo drug application, electrical stimulation, or kindling of the amygdala (McNamara, 1995).

Various useful animal models for epilepsy research include the systemic or intracerebral injection of kainic acid (Cronin and Dudek, 1988) and other epileptogenic agents [pilocarpine, n-methyl-D-aspartate (NMDA), picrotoxin,
pentylenetetrazol, zinc, aluminum, cobalt, strychnine] (Sagratella, 1998; Krall et al., 1978; Priel et al., 1996; Kreindler, 1965) and intracerebral injection of tetanus toxin (Jefferys et al., 1995), ferric cations (Doi et al., 2000). Besides these commonly used agents, penicillin, an antibiotic of common use can be used (on repeated application) to produce chronic epileptic animal without having any side effects. Also this model aptly mimics human generalized epilepsy (Sarkar, 1970; Assai et al., 1995).

Some of the more useful models of epilepsy research are listed below.

1. Monkey model of absence (petit mal) seizures

A complete description of the behavioural arrest reaction together with the spike and wave after discharge in the electroencephalograph (EEG), obtained by thalamic stimulation in juvenile monkeys with bilaterally symmetric aluminium hydroxide focal implants in anterior premotor cortical areas has been reported (David et al., 1982). This primate model of absence seizures is based on the conceptual approach of Gloor (1979), who showed that the spike and wave EEG pattern represented an abnormal cortical response to normal afferent thalamo-cortical volleys during generalized penicillin epilepsy of the cat. For experimental models to be considered relevant to human condition certain criteria are to be satisfied (Myslobodsky, 1976) — (1) must be time locked to the behavioral event characterizing ‘absence’ and the duration of disturbance of consciousness should be comparable to that in man, (2) must be evoked by the same activating conditions as in man. viz., light sleep, photic stimulation and hyperventilation, (3) should ensure that the chronological age of monkey surrogates coincides with that of human patients, (4) should establish that the EEG spike and wave pattern should be abolished by interference with integrity of thalamo-cortical pathways, (5) should emerge spontaneously. The monkey model of absence seizures satisfies these
stringent requirements. Also morphologic similarities of simian and human EEG and behaviour patterns render it useful for laboratory screening of antiabsence agents (David et al, 1972; 1982).

2. Aluminium hydroxide induced partial or secondary generalized (grandmal) seizures in monkeys

Of the available laboratory methods modelling focal epilepsy, that induced by intracortical injection of aluminium hydroxide, Al(OH)₃, is considered most analogous to the human condition (Jasper, 1972). Following injection of Al(OH)₃ into motor cortical areas, the clinical pattern of seizures is characteristic of the location of the neuronal cicatrix or scar tissues as in human epilepsy of focal onset (David and Grewal, 1977). Initially, seizures are focal and progress by Jacksonian spread to involve the entire body musculature and later become secondarily generalized (David and Grewal, 1977a, 1977b). During this phase, powerful tonic jerking, salivation and loss of consciousness are evident. Unlike rodents subjected to MECS, the tonic hindlimb extensor phase is not prominent in monkeys. In most animals, once the seizures are established they recur spontaneously and chronically.

3. Experimental temporal lobe epilepsy in monkeys

In contrast to considerable experience and information generated on the previous two monkey models, only limited knowledge concerning primate models of temporal lobe epilepsy (TLE) is available. Probably because of the difficulty in producing a chronic animal model of TLE, neuropharmacological approaches in temporal lobe epilepsy have largely been restricted to acute seizures VIZ., electrical stimulation of the hippocampus in conscious cats, or more recently, the hippocampal slice preparation in guinea pigs (Oliver et al, 1977). In this method Al (OH)₃ is stereotaxically injected into the deep structures of the temporal lobe of monkeys according to Mayanagi and
Walker (1974). The monkey receives injections into the pre- and postcentral gyri or the arachnoid space around the central sulcus. Seizures in such lesioned monkeys are readily precipitated by metrazol, but spontaneous seizures are rare. A characteristic behavioural change occurring 8 to 12 months after hippocampal Al(OH)$_3$ injection is the appearance of marked aggression. The aggression is inappropriate and misdirected (e.g. no face-to-face angry encounters but directed to the back of humans, dashing forcefully on cage bars or vicious biting of the restraint chain). Experimental results indicated a loss of GABAergic inhibitory synapses at the epileptic foci. The loss of inhibitory GABAergic neurons is hypothesized to cause epileptic activity of cortical pyramidal neurons.

Experimental epileptic models can also be prepared with rats, cats, gerbils etc.

4. Pilocarpine model

Systemic administration of the cholinergic agent pilocarpine, induces spontaneous seizures (Priel et al, 1996). Experiments demonstrate that structural damage of the brain leads to spontaneous recurrent seizures. The characteristic of the seizure resembles human partial epilepsy. In rats, a behaviour (akinesia, facial automatisms, limbic seizures consisting of forelimb clonus with rearing, salivation, masticatory jaw movements, and falling) and EEG changes (significant theta rhythm and isolated spikes in hippocampus, synchronization of the activity in hippocampus and cortex. EEG seizures, status epilepticus) are observed.

5. Kainic acid model (Arias et al, 1990; Poli et al, 1985)

Kainic acid injections destroy hippocampal pyramidal cells; induce recurrent collateral sprouting of the hilar mossy fibres, and lead to chronic seizures. Recording from CA1 showed a reduction in inhibition, leading to epilepsy. A recurrent excitatory
loop among CA3 pyramidal cells forming a positive feedback in the normal hippocampus may also enhance the propensity for seizures.

6. Penicillin model

Penicillin was one of the first topical convulsants to be studied (Walker and Johnson, 1945; Prince, 1969). Walker’s school systematically studied the epileptogenic effect of penicillin by administering locally at different regions of the cortex and subcortex (Lichtenstein et al, 1959; Walker and Richter, 1963, 1966, Walker and Serrano, 1963; Walker and Rivera, 1964). Penicillin is still considered the most suitable agent for the production of experimental epilepsy (Biziere and Chambon, 1987; Fisher, 1989) particularly from the possibility of using it for inducing a chronic epileptic process (Maiti et al, 1968; Sagratella et al, 1985; Kryzhanovskii et al, 1992; Horn and Ebeling, 1993; Ferraro et al, 1994 b; Horn et al, 1995; Horn and Gehring, 1996; Horn, 1996; El-Yamani and Horn, 1999; Purkayastha and Guha, 2001, Hazra and Guha, 2003 a). The epileptogenic lesion produced by penicillin is known to be confined strictly to the desired nervous structures and is capable of rapid onset of epileptic phenomenon (within ½ hour after operation) in the chronic unrestrained unanaesthetised cats; furthermore, this epileptic activity may last for about one month (Sarkar, 1970). Horn and Weber (1993 a, b) studied the principles of penicillin-induced focal epilepsy (PCN-EA) in awake rats. During PCN-EA, the pattern of focal activation was found to change depending on the site of the primary focus. A focus within the motor cortex induced a mirror focus in the contralateral hemisphere. A focus within the hippocampus induced a multifocal pattern which shifted between the motor and occipital area. Regarding the mechanism of action of penicillin, penicillin is believed to work by blocking synaptic inhibition mediated by the GABA\textsubscript{A} receptors (Jefferys, 1993). Similar actions have been found with the more specific and potent
blockers of GABA\textsubscript{A} responses, bicuculline and picrotoxin. The convulsant drug most often used for drug screening, PTZ, probably also works by blocking GABA\textsubscript{A} receptors (Leweke et al, 1990). Penicillin is capable of inducing very different experimental epilepsy when injected systematically or applied to the brain \textit{in vivo} in very low doses (compared with those used to block inhibition). Under these conditions, cats develop a 3 per second spike-and-wave EEG, which models the primary generalized epilepsy, absence or petit mal (Gloor and Fariello, 1988).

The modulation of cerebellar Purkinje cell activity and EEG from parietal centre was studied in rat model of epilepsy induced by penicillin under acute haloperidol and amphetamine treatment (Culic et al, 1994). However, all parts of the brain are not equally susceptible to stimulation; some more than the others. From previous experiments in our laboratory it has been found out that penicillin when topically applied in the somatosensory area results in typical epileptogenesis.

Regarding the relationship of epilepsy and doses of penicillin, it has been observed that application of very high dose of penicillin in layer IV of somato sensory area results in appearance of evoked potentials and spontaneous epileptiform discharges (Bashir and Holmes, 1993). However Sarkar (1970) has shown that 100 IU is sufficient for the generation of epileptogenesis by PCN when applied topically in the somatosensory cortex.

Mameli et al, 1999 have carried out investigations to find the sensitivity and electrophysiological patterns of paroxysmal activity induced in different brain structures by topical application of penicillin-G in rats as far as the features of the paroxysmal activity was concerned, significant differences among tested structures were observed. In particular within the somatosensory cortex the main differences were represented by
the gradual increase in burst frequency and voltage from the surface to the IV layer and by their subsequent decrease in deeper layers (V to VI). In the diencephalons the paroxysmal activity was similar to that observed in more superficial and deeper cortical layers even though epileptic burst showed lower amplitude.

Their results show that the neuron structures tested with penicillin-G had a different epileptogenic sensitivity and response pattern which significantly change along the cerebral cortex - spinal cord axis. The highest epileptic sensitivity was observed in somatosensory centre at 500-600 microns depth; in the other cortical layers, a significant lengthening in latency was observed. Among the other structures the spinal cord seemed to be the most sensitive target to the epileptogenic action of penicillin-G, whereas in the remaining structures, sensitivity significantly decreased in rostro-caudal direction.

7. Pentylenetetrazol (PTZ) model

PTZ is a widely used convulsive substance in experimental epilepsy (Lösch et al, 1991; Woodbury, 1980). Most studies involve systemic application to produce generalized epileptic activity and only rarely it is applied locally. In local applications, push-perfusions (Velasco et al, 1985), local superfusions (Bures et al, 1975; Kent and Webster, 1986) or microinjections of PTZ (Banerjee et al, 1970) induce focal internal discharges. Systemic PTZ induced epileptogenesis simulate human myoclonic (absence petitmal) epilepsy (Lösch and Schmidt, 1988).

8. Kindled seizures in rats

Kindling triggered by stimulation in the limbic systems is one of the most extensively studied forms of experimental epilepsy and has been proposed to be analogous to complex partial epilepsy in humans. (Girgis, 1981; McNamara, 1984). The progressive development of seizures due to repeated, low-intensity, local brain stimulation is referred to as the ‘kindling effect’. Graham Goddard coined the term
'kindling' because of the analogy to lighting a fire and recognized its potential as a model of human epileptogenesis (Goddard et al, 1969). In rats, amygdaloid stimulation elicited focal electrical seizure activity with an EEG after discharge pattern, but no visible seizure (Morimoto et al, 1987). Subsequent daily stimulation induces the development of kindled seizures, generally evolving through stages as classified by Racine (1972). Kindling differs from many of the other chronic experimental epilepsies in that it does not necessarily involve convulsant drugs. Its essential feature is the repeated presentation of some kind of stimulus. In the kindling model of epileptogenesis, periodic application of an initially subconvulsive electrical stimulus eventually leads to the permanent establishment of an epileptic state (McNamara, 1995; Silver et al, 1991; Racine, 1972; Racine, 1978; Schwartzkroin, 2002). Kindling is established once a class 5 seizure has developed and thereafter, seizures remain stable over time. This model is reliable and convenient, responses are easily measured and animals can be tested repeatedly with different drugs and doses. Thus, full amygdaloid kindled seizures in the rat may simulate petitmal rather than grand mal, at least in the initial phase of the kindling process (Callaghan and Schwark, 1980). Numerous variations have been reported since 1969 when Goddard et al first described a kindling model in the rat Amygdala (Goddard et al, 1969). Examples include using the kindling model in cats (Wada et al, 1976) as well as the electrical stimulation of the ventral hippocampus or angular bundle (Shirasaka and Wasterlain, 1994; Halonen et al, 1996). Kindling can also be obtained by administration of subconvulsive doses of chemicals such as PTZ (Mason and Cooper, 1972; Becker et al, 1992, 1996), FG 7142, a benzodiazepine receptor inverse agonist (Little and Nutt, 1984), and other substances (Wasterlain and Jonec, 1984; Wasterlain et al, 1989).
9. Perforant-Path stimulation model

Implanted electrodes that stimulate the perforant path fibers to the hippocampus (2Hz and 20V for 24hr) induce seizures in rats. Experimental studies indicate the formation of basal dendrites on the rat granule cells. This is consistent with the fact that epileptic patients have more granule cells, which possess basal dendrites.

10. Audiogenic model (Cole et al, 2002)

Rats can be genetically selected to exhibit severe generalized motor seizures in response to intense auditory stimuli. Studies have indicated that the epileptic activity arises from the inferior colliculus. A loss of GABA-mediated inhibition is theorized to cause the seizure. An infusion of GABA agonists into the inferior colliculus attenuates the seizures.

11. Genetic models

(a) Epileptic Gerbils

The Mongolian gerbil (Meriones unguiculatus) has been phenotypically bred to produce a seizure-sensitive strain. The animals exhibit spontaneous seizures when introduced into a novel environment after 50 days of age. Experiments done with seizure-sensitive gerbils indicates an increase in GABAergic neurons in the dentate gyrus. It is theorized that the GABAergic terminals may synapse with other inhibitory basket cells, and thus disinhibit granule cells.

(b) Genetically Epilepsy Prone Rats - GEPRs

Seizure predisposition in the GEPRs is characterized by abnormal sensitivity to a number of seizure-provoking stimuli. GEPRs have lower threshold for electrically induced seizures and for seizures induced by a number of chemical convulsants (Jobe

On NTs’ involvement in basic mechanisms of the epilepsies

Evidences are accumulating to support a relationship between central nervous system transmitters and convulsions (Schlichter et al, 1986). Considerable emphasis has been given to studying the cerebral metabolism of the biogenic amines in view of the possibility that affective neuronal and psychiatric disorders may be associated with abnormalities in their metabolism. Currently a great deal of interest is centred on the possible involvement of certain amino acids in the mechanism of epilepsy. This is partly the result of an awakening in neurophysiology to the paradox that a range of simple and ubiquitous amino acids which are involved in a wide range of metabolic pathways in the CNS are likely also to function as major synaptic transmitters in the brain and spinal cord.

Serotonin and noradrenaline strongly influence mental behavior patterns, while dopamine is involved in movement. These three substances are therefore fundamental to normal brain function. For this reason they have been the center of neuroscientific study for many years (Blows, 2000).

Close relationship exist between diminished brain nor-adrenergic activity and endogenous depression. Noradrenergic over activity, central and peripheral, appears to be involved in manifestation of anxiety and production of tremor (Eadie and Tyrer, 1983).

It has been hypothesized that there is an inverse relation between seizure predisposition and levels of noradrenergic activity in brain (Jobe et al, 1994). Brain
stem seizures (tonic and clonus extensor convulsions) are characterized by innate noradrenergic deficits and from selective lesioning of noradrenergic neurons and/or pathways (Mishra et al, 1994).

The increase or decrease of norepinephrine (NE) level with epilepsy is area specific. An increase in seizure severity is always associated with marked depletion of NE in the midbrain excluding the inferior colliculus (Wang et al, 1994).

Interestingly norepinephrine (NE) has been proposed to have both pro and anti convulsant properties (Rutecki, 1995). On the other hand DA has an antiepileptic action. It inhibits most hippocampal neurons. The traditional anticonvulsant action of DA was attributed to D-2 receptor stimulation in the forebrain, while the advent of selective D-1 agonist with proconvulsant properties revealed that DA could also lower the seizure threshold from the mid brain (Benardo and Pedley, 1985; Starr, 1996). The inhibitory effects of DA are derived from induction or enhancement of a calcium activated K⁺ conductance (Benardo and Pedley, 1985).

Cavalheiro et al (1994) reported that after pilocarpine administration in rats, hippocampal NE level was decreased whereas dopamine (DA) content increased. Utilization rate measurement of monoamines showed increased NE consumption and decreased DA consumption. Considerable body of evidence has indicated that the noradrenergic system provides the forebrain with substantial protection against the development of seizure activity. This NE protection occurs in several seizure models (Mason and Corcoran, 1979) and is observed most dramatically when the NE terminals have been degraded by central nervous system application of 6-hydroxydopamine (6-OHDA) (McIntyre and Edson, 1989). In cases of kindled seizures, such depletion of NE results in rapid development of generalized convulsive behaviour (Corcoran and
Mason, 1980; McIntyre and Edson, 1985; McIntyre and Giugno, 1988). Conversely, increasing NE activity by stimulation of the locus coeruleus (LC) (Jimenez-Rivera et al, 1987) or by pharmacological treatment (McIntyre and Giugno, 1988; McIntyre et al, 1982) retards the development of kindling. These seizure inhibitory effects of NE on the development of kindling, however, are slight or nonexistent if seizure has previously occurred (Westerberg et al, 1984). Mohr and Corcoran (1981) had reported of an accelerated rate of kindling in the amygdala, hippocampus and neocortex after NE depletion. In rats two weeks after amygdaloid kindling a significant depletion of noradrenaline has been found in the ipsilateral frontal cortex. In the same rats a significant depletion of serotonin was observed in the stimulated amygdala and contralateral hypothalamus, but no significant change in the concentration of dopamine was found (Lewis et al, 1987).

However contradictions are never hard to find in science.

Shouse et al (2001 a, b) has reported of significant increase of NE, DA and 5-HT in the amygdala only during focal after-discharge (AD) in young cats subjected to amygdala kindling. In the same animals these neurotransmitter levels had increased in both the amygdala and LC during generalized AD. In rodents, both DA agonists and antagonists have been found to be ineffective against either electroshock or chemically induced seizures, nor did they affect the development of amygdaloid kindling (Meldrum et al, 1986). When 6-hydroxydopamine, which depletes norepinephrine, was injected intraventricularly in the tottering mouse the spike wave discharges and absence like seizures disappeared (Noebels and Sidman, 1979). On the contrary, low levels of dopamine in lumbar CSF in epileptics (Hiramatsu et al, 1987) and in epileptic foci in human brain have been observed (Mori et al, 1987). Again in focal epileptic cases it has been shown that in the temporal neocortex, the focal area has increased levels of NE.
DA, dihydroxyphenylalanine (DOPA), 5-hydroxyindole acetic acid (5-HIAA) and homovalinic acid (HVA) (Goldstein et al, 1988; Louw et al, 1989). In some studies forebrain concentrations of NE and DA have been found to be unchanged after kindling (Siegel and Murphy, 1979; Stock et al, 1983; Westerberg et al, 1984) whereas in other experiments localized depletion of NE (Callaghan and Schwark, 1979) or widespread depletion of both NE and DA (Racine, 1972) was observed.

Histamine also is believed to affect neurobehavioural disorders such as alzheimer’s disease, down syndrome, attention deficit hyperactive disease, epilepsy, parkinson’s disease etc. (Onodera and Miyazaki, 1999). CNS HA has been suggested to participate in seizure control. Intracerebroventricular (ICV) administration of HA decreased seizure susceptibility on electrically and pentylenetetrazol-induced convulsions significantly and dose dependently. While centrally acting HA H1 antagonists such as pyrilamine (or mepyramine) and ketotifen antagonized the inhibitory effect of HA (Yokoyama et al, 1994 a, b).

Antagonists of the HA H3-receptor (thioperamide and burimamide) are reported to potentiate the severity of clonic convulsions induced by picrotoxin while impropidine (ICV) an antagonist with H2-agonist activity, inhibited leptazol-induced seizures. The H3-agonist, (R) alpha-methylhistamine, potentiated chemically-induced seizures, but at lower doses there was slight inhibition (Sturman et al, 1994).

Histaminergic neuron system is also believed to be involved in inhibition of seizures associated with febrile illness in childhood. The increased susceptibility to seizures during fever is hypothesized to be connected to the lack of increase in CSF HA in the febrile convulsive group (Kiviranta et al, 1995).
The inhibitory action of HA especially in the amygdaloid kindled seizures is suggested to be closely associated with the actions of GABA (Ishizawa et al, 2000). Activation of GABAergic transmission within the substantia nigra has been shown to suppress several forms of generalized seizures in experimental models of epilepsy (Depaulis et al, 1990).

It is also now clear that the proconvulsant antibiotic penicillin works by blocking synaptic inhibition mediated by the GABA receptors. Similar actions have been found with the more specific and potent blockers of GABA responses, bicuculline and picrotoxin (Jefferys, 1993). The convulsant drug most often used for screening, PTZ, probably also works by blocking GABA receptor (Leweke et al, 1990).

Upon stimulation of GABAergic system decreases in cellular excitability is observed which leads to control of seizures in practically all animal models of epilepsy. GABA receptor agonists have a wide spectrum as they antagonize not only seizures which are dependent on decreased GABA synaptic activity but also convulsion states which are apparently independent of alterations in GABA mediated events (Bartholini, 1985).

**Epilepsy and neuron loss**

Seizure disorders have always been associated with a complex mixture of psychopathology. Never has sufficient attention been laid on the extent of structural damage that is associated with the disorder.

The observation, made by Bouchet and Cazauvieilh in 1825 of a palpable hardening and atrophy of the uncus and the mesial temporal lobe in patients with epilepsy did not attract much attention until Sommer (1880), some 50 years later.
described neuron loss in a particular area of the pyramidal cells of the hippocampus in relation to epilepsy. However Sommer concluded the sclerosis to be the cause of epilepsy. The concept of the nature of ammonshorn sclerosis (Sommer, 1880) reached a new stage with the delineation of psychomotor epilepsy (Gibbs et al, 1948; Bailey and Gibbs, 1951; Earle et al, 1953; Penfield and Jasper, 1954; Falconer et al, 1955).

Subsequent studies (Seitelberger, 1969) have tried to reverse this hypothesis but still the older idea of epilepsy- a functional disorder without any consequent structural damage prevailed (Townsend, 1976).

**Epilepsy and nucleic acid modification**

For deeper understanding of the mechanism of epilepsy a clear picture about the nucleic acid modifications due to the disorder is essential. It has been reported that recurrent limbic seizures caused a massive, delayed, and reversible reduction in levels of the kainite receptor mRNA in dentate gyrus; lesser decreases were found in pyramidal cell fields of hippocampus and superficial cortex (Gall et al, 1990). Also nucleic acid fragmentations are markers for neuronal damage (Cole et al, 2002). Therefore it is essential to note changes, if any, in the levels of DNA and RNA- the major molecular constituents of the eukaryotic chromosome during epileptogenesis.