Chapter IX
GENERAL DISCUSSION

1. Introductory Remarks

It is beyond the scope of this present text to discuss all the aspects of epilepsy, which like various other diseases is a multifactorial heterogeneous entity. So to do justice to this study only a few relevant parameters influencing epileptogenesis are reflected in relation to the different experimental epileptic models in the present work.

Being a multifactorial and multifaceted disorder ambiguities are not rare regarding the causal factors, symptoms, traits and prophylaxis. Striking differences in opinion on the particular factors responsible for the disorder arise from different outlooks on certain fundamental aspects of the disease.

2. Review of Reviews

For the last several decades there have been enormous studies regarding the evolution of epilepsy. Studies revealed a critical interplay between a set of excitatory and inhibitory neurotransmitters at all stages of epilepsy. The two common CNS transmitters that have repeatedly been studied in a number of epileptic models are glutamic acid (Lason, 1998) and GABA (Benardo and Pedley, 1984). Since early 19th century, a number of investigations involving lesion and stimulation of CNS areas have demonstrated the significance of neurotransmitters in epilepsy (Goddard et al, 1969; Jobe et al, 1994; McNamara, 1995; Silver et al, 1991; Racine, 1972; Wang et al, 1994). Considerable literature links neurotransmitters with epileptogenesis (Schlichter et al, 1986; Shouse et al, 2001 a). Seizure disorders are thought to reciprocally affect monoamines (Engel and Sharpless, 1977; Sato and Nakeshma, 1975; Shouse et al,
Persistent changes have been reported after kindling, which is characterized by transient synaptic effects on distal structures and related functions (Corcoran, 1981; Engel and Sharpless, 1977; McIntyre, 1981; Okada et al, 1997). Short-term post-kindling changes have been reported to be usually consistent and characterized by increased monoaminergic concentrations during seizures followed by depletion (Corcoran, 1981; Dazzi et al, 1997; During et al, 1992; Kaura et al, 1995; Kokaia, 1994 a, b; Löscher and Honack, 1995; Serra et al, 1997; Wada et al, 1997).

However there are numerous contradictory notes regarding this aspect (Lewis et al, 1987; Wang et al, 1994; Ferraro et al, 1994 a; Yan et al, 1994). In some studies fore-brain 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. Other investigators have described depletion of 5-HT restricted to the midbrain shortly after completion of amygdaloid kindling (Mohr and Corcoran, 1981).

Findings of long-term post-kindling changes are also inconsistent (Corcoran, 1981; McIntyre, 1981; Shouse et al, 1994). Some authors reported rebound increases in monoamines and other neurotransmitters (Dazzi et al, 1997; Cedarbaum and Aghajanian, 1978; Corcoran, 1981; During et al, 1992; Kokaia et al, 1994 a, b; McIntyre et al, 1999), some report chronic suppression (Engel and Sharpless, 1977; Shouse et al, 1994) and some report no long-term changes at all (Corcoran, 1981; McIntyre, 1981). Several factors could contribute to these discrepancies. Examples are differences in epileptic paradigm, species and age of animals as well as severity of seizure disorder, duration and/or timing of post seizure follow-up.
Therefore it seemed pertinent to make an attempt to study how amygdaloid kindling, PCN and PTZ induced seizure activity which mimics human generalized convulsions alters some of the brain's very important neurotransmitters and the associated nucleic acid variation, electroencephalographic and behavioural components.

3. Rat as an Animal Model for Epileptogenesis

Animal models of neurological deficits are essential for the assessment of new therapeutic options. A comprehensive homology can be drawn between rats and primates regarding motor patterns. Also rat models of hemiplegia, neglect and extinction are useful in assessing the outcome of ischaemic or traumatic brain injury, and monitoring the effects of therapeutic interventions (Cenci et al, 2002). The rat model is an indispensable tool for understanding the aetiology, pathogenesis and complications of seizure disorders. Last but not the least, rats being economical they, fit the budget.

4. PCN, PTZ and Amygdaloid kindling Epileptogenesis – How Appropriate are the Models?

Although numerous models of epileptogenesis are available for research (Temkin, 2001; Temkin et al, 2001) very few accurately simulate human epilepsy. Cortical PCN injection and systemic PTZ injection paradigms are two such models which reflect human generalized (Gloor and Fariello, 1988; Witte, 1994; Ferraro, 1994 b) and myoclonic (absence petitmal) epilepsy respectively (Lösch and Schmidt, 1988). Amygdaloid kindling paradigm mimics human temporal lobe epilepsy and complex partial seizure (Sato et al, 1990; Goddard, 1969; Girgis, 1981; McNamara, 1984).
5. Results

An overall analysis of the results of all the chapters clearly demonstrates that PCN, PTZ and amygdaloid kindling induced epileptogenesis of albino rats resulted in significant alteration of brain transmitters associated with increased seizure-related behavioural activities in the acute as well as in the chronic conditions. The rats remained in good health and weight throughout the observation period. There were some deviations of feeding and drinking behaviour from that of control and sham operated animals; however the factor was probably not of utmost significance to the overall well-being and recovery of the epileptic animals. The present study shows that exposure to intracortical penicillin in the somatosensory cortex of the rat, PTZ (i.p.) and amygdaloid kindling produces behavioural and electroencephalographic changes as well as differential changes in the levels of monoamines in different regions of the brain.

i.) Behavioural and Electroencephalographic changes:

Behavioural Modifications

The present study revealed that systemic injection of PTZ and intracortical injection of PCN in albino rats resulted in an immediate onset of seizure predisposition followed by general convulsions, tremors, temporary postural asymmetry and several other symptoms of epilepsy.

After recovery from anaesthesia the animals were unable to stand or walk, very often they showed circling, rotating or barrel movements. All the symptoms of unstabilized deficiency like lying in their abdomens with hind limbs extended or leaning to one side and circling movements were commonly observed. Hyperextensions of fore limbs were occasionally observed. During the convulsive phase the animals lost their righting reflexes and often showed jerky or jumpy movements, throwing of the body in either direction were noticed. The sequence of such convulsive phenomenon did
not persist for a long time and rarely recurred beyond 3-4 hours after PCN or PTZ application. The behavior deficits observed in these two epileptogenic models (PCN and PTZ) appeared similar to human generalized and myoclonic (absence petitmal) epilepsy respectively. Amygdaloid kindling in rats did not result in seizure manifestations immediately after stimulations although behavioural manifestations like eye-twitching, gustatory movement and jaw movement were evidenced indicating development of kindling. However in fully kindled rats generalized seizures were observed.

**Electroencephalographic Modifications**

All the animals made experimentally epileptic developed epileptic EEG activity. The rats showed spontaneous recurrent epileptiform discharges consisting of bursts, spikes and multiple spike wave complexes. The time course of the build-up and progression of epileptic EEG features were consistent with previous reports (Singh and Pathak, 1990; Moriwaki et al, 1990; Moriwaki et al, 1992). During the inter ictal phase the animals became highly responsive to any type of sensory stimulation either mechanical (pinching), photic or auditory stimulation. Repeated clapping resulted in an increase of sharp waves and spikes along with focal or generalized seizures. The penicillin induced epileptic group showed irregular, isolated large amplitude discharges or single spikes were followed by synchronous regular high voltage discharges. Isolated spike discharges were observed within 15 minutes after PCN application which gradually built up into synchronous high voltage generalized seizure discharges within 70-95 minutes. These findings were consistent with prior reports of Neuman, (1986) and Sullivan and Osorio, (1991) that application of penicillin in cerebral cortex resulted in the appearance of focal epileptiform activity and multiple synchronous spikes after intraperitoneal administration of penicillin.
Within 1-2 minutes after PTZ application in the rats there was increase in frequency followed by lowering of the amplitudes of the waves. Within 10-20 minutes after PTZ application EEG recordings were marked with spikes, waves and domes and gradual lessening of the interseizure period.

Daily stimulation at the basolateral amygdala of all the animals produced the same progressive development of Afterdischarge (AD). Seizure discharges were observed in amygdala and the frontal cortex from the second day. During stage one kindling the duration of ADs was not more than 10 seconds. The duration of AD gradually increased (15-60 seconds) with subsequent stages (stage 2-5) of kindling.

ii.) Catecholaminergic Modifications:

It is evident from the results that epileptogenesis induced by PCN, PTZ as well as amygdaloid kindling significantly alters the brain NE and DA levels. However the changes are brain area and time course dependant. In our study penicillin significantly increased DA level in the cerebral cortex and midbrain but decreased in the cerebellum and caudate nuclei. The role of dopaminergic system in epileptogenesis has been generally neglected because DA does not have any effect on development of kindling (Callaghan and Schwark, 1979; Campos and Cavalheiro, 1986; Corcoran and Mason, 1980) neither is DA level altered in GEPR (Jobe et al, 1986). However in other experiments widespread depletion of both NE and DA (Racine, 1972) was observed. Contrarily 62% increase in the DA concentration in amygdala has been observed during focal afterdischarge (Shouse et al, 2001a, b). In the present study also, 15 days after amygdaloid kindling a significant enhancement in the DA level was observed in the cerebral cortex however no comparable change in the DA level was observed in the cerebellum, caudate nuclei and the midbrain. 30 days after the last kindled seizure DA level in all the areas were closer to the sham control base line.

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suggesting amygdaloid kindling results only in short-term modifications in the dopamine level. The results are in corroboration with other studies where DA agonist apomorphine has been suggested to have an anti-convulsant action against sound-induced convulsions in mice (Anlezark and Meldrum, 1975) and against photically induced seizures in baboons (Meldrum et al, 1975). The levels of DA and HVA were higher in the epileptic focus in human temporal cortex as compared with the nonfocus tissue (Pintor et al, 1990), and use of apomorphine has been suggested for treatment of myoclonic epilepsy in humans (Quesney et al, 1980). The partial decrease accompanied by compensatory changes can be attributed to the fact that DA which preponderates in the corpus striatum, including the caudate nucleus and the putamen of the lentiform nucleus is believed to act as an inhibitory transmitter in the basal ganglia, but in some of the other areas of the brain it is possibly excitatory.

The increase in the cortical epileptic activity of the PCN-induced epileptogenic focus observed in the present study is similar to the increase found in the Fecl₃-induced chronic model of epilepsy (Sharma and Singh, 1999). The hyperexcitation as is observed in this study can result from a decrease in the overall noradrenergic activity. NE depletion has been associated with increased seizure susceptibility in most experimental models of epilepsy (McIntyre and Edson, 1982; Mason and Corcoran, 1979; Wu et al, 1987). Trottier et al (1981), also reported a 40% reduction in cortical NE levels compared to control as well as sham control rats during epileptic period in cobalt-induced epileptic model. In the same model NE level was shown to return to normal level after the extinction of epileptic syndrome. NE has been proposed to have both pro and anti-convulsant properties (Rutecki, 1995). In this study, an inverse relation between acute chronic PCN induced seizure predisposition and level of NE activity is observed in the cerebellum, midbrain and caudate nuclei. However a direct
relation between the two is observed in the cerebral cortex in the 15 days chronic PCN case. However in the acute PCN and 15 and 30 days amygdaloid kindling models NE level had decreased which can be corroborated with the results of that of Lewis et al. (1987) and Westerberg et al. (1984) which suggests NE’s suppressive action is limited to seizure development per se and depletion of NE does not affect established seizure. Similar to our results Jobe et al. (1982 a) reported a decrement of NE in the telencephalon, hypothalamus, midbrain, pons-medulla and spinal cord in genetically epilepsy prone rats (GEPRs). Shouse et al. (2001 a) again reported of elevated level of amygdaloid NE during increased seizure activity as compared to the pre-kindling baseline. NE usually functions as an excitatory neurotransmitter. This system spreads virtually to every area of the brain but the principal cell bodies are positioned in the L.C, located at the juncture between the pons and the mesencephalon. Intracortical application of PCN possibly stimulates the cortical cell and this excitation passes to widespread areas of the brain by its intricate anatomical connections. It is possible that the initial insult of seizure due to PCN results in depletion of NE due to increased utilization of the transmitter. However prolonged seizure activity causes excitation of RAS and the sympathetic system which in turn results in liberation of epinephrine/NE that stimulate the mesencephalic portion of RF that runs upward to the subthalamus and projects diffusely to the cerebral cortex (Guyton, 1991). The negative feedback stimuli thus produced, suppresses the excitability of the cortical neurons. This is probably responsible for the increased NE level in chronic epileptic cortex as is observed in the present study.

iii) Serotonergic Modifications:

It is evident from the results that experimental induction of epileptogenesis by PCN, PTZ and amygdaloid kindling had resulted in significant modifications in the
serotonergic system. The 5-HT level had decreased in the cerebellum, caudate nuclei and midbrain in the acute, as well as in the 15 and 30 days PCN chronic group. In the cerebral cortex however an increase in the 5-HT level was observed in all the PCN and PTZ groups. Such regional variations in the transmitter’s level are again probably due to the complex brain anatomical and functional connections. In the midbrain and caudate nuclei PTZ had lowered 5-HT significantly. In fully kindled rats, 15 days after the last kindling stimulation, there was a decrease in the 5-HT concentration in the midbrain, caudate nucleus and cerebellum, however there was no significant change of the neurotransmitter in the cerebral cortex. No significant change was found in 5-HT content 30 days after the last kindled seizure. Our results are again in corroboration with the results of Lewis et al (1987)-reported of short-lasting depletion of amygdaloid and hypothalamic 5-HT, followed by a late–appearing depletion of hippocampal 5-HT. Jobe et al, (1982 b) reported of decreased 5-HT levels in various brain regions of genetically epilepsy prone rats as is seen in our study.

Similar observations have been reported in different experimental epileptic models. The fact indicates that PCN epilepsy has differential effect on CNS 5-HT level. Munkenbeck and Schwark (1982) found a decrease in level of 5-HT in the contralateral hypothalamus of amygdaloid kindled rats. Epileptogenic foci in humans have increased concentrations of 5-HIAA (Goldstein et al, 1988). Schreiber and Schlesinger (1972), have found decreased concentrations of 5-HT in the diencephalons and brainstem of F1 hybrid strain mice. The principal cell bodies of 5-HT neurons are localized in the raphe nuclei of the lower brain stem but project throughout the brain and spinal cord. The serotonin released in the cerebrum almost certainly tries to play an essential inhibitory role to counteract the PCN induced hyperexcitation.
It is well known that there is a direct control of brain activity by specific transmission of nerve signals from the lower brain areas to the cortical regions of the brain. The neurotransmitters also take active part in the control of brain activity. There is release of excitatory and inhibitory transmitters into the brain regions in response to nerve signals. It is possible that PCN, PTZ and amygdaloid kindling directly stimulate the cortical cells. This excitation passes down the cortex to widespread areas of the brain and excites all three neurotransmitter systems i.e. NE, DA and 5-HT differentially causing liberation of NE, DA and 5-HT at different terminals. From our results it is evident that abnormalities in specific neurotransmitter system play important role in epilepsy. Simultaneous decrease in the levels of DA, NE and 5-HT has also been reported in various other experimental epileptic models. Such regional alteration in the levels of monoamines is probably due to the anatomical and functional connections of the bioaminergic pathways. The results suggest a strong interaction between the different groups of neurotransmitters during epilepsy. It can be suggested that PCN, PTZ and amygdaloid kindling exert their convulsive action by modulating these monoamine levels.

iv) Histaminergic Modifications:

There exist some evidences of involvement of neurotransmitter systems with development and/or prevention of kindling (Kalichman, 1982). A number of studies have suggested that histamine plays an important role in the pathogenesis of seizure disorders. For example, Scherkl et al (1991 a) found that histidine increased the threshold for pentetrazol-induced seizures. Further evidence of the involvement of histamine has been derived from studies in which drugs that deplete brain histamine have been found to increase the duration of clonic convulsions induced by maximal electroshock (MES) in mice (Yokoyama et al, 1992). In the present study, it was found
that there was a tendency for reduced histamine content in the cerebellum, midbrain and caudate nuclei, in the 15 days chronic PCN treated rat brain except an increase in the cerebral cortex. Similar results were observed for the PTZ group as well. In the acute PCN group there was an increase of HA in the cerebral cortex but this raise was of a much lower extent when compared to the 15 days PCN group.

In the amygdaloid kindled group 15 days after the last kindled seizure, significant decrease in the HA level was observed in all the brain regions studied viz. cerebral cortex, cerebellum, caudate nuclei and midbrain.

No significant change was found in HA content one month after the last kindled as well as PCN induced seizure.

Toyota et al (1998) reported significant decrease in histamine level in the bilateral amygdala, hippocampus and diencephalons one hour after last kindled seizure. The histidine decarboxylase (HDC, a histamine synthesizing enzyme) activity of the bilateral amygdala and diencephalons are reported to be lower in the kindled group than in the control group. The results may reflect not only the developed seizure susceptibility, but also the seizure itself and the effect of the PCN and electrical stimulation.

Our results are also in line with clinical reports that H1 antagonists (antihistaminics) occasionally induced convulsions in epileptic patients and healthy children (Yokoyama and Inuma, 1996). It has been reported that over dosage of anti-histamine agents causes convulsion, especially in children of pre-school age (Bernstein and Discant, 1982; Churchill and Gamonn, 1949; Mueller, 1983; Schwartz and Patterson, 1978; Wyngaarden and Seevers, 1951). These clinical reports are in corroboration with our findings in epileptic models and indicate a conceivable role for central HA in convulsions. The diminution of brain HA level in epilepsy is probably due to some alterations in other messengers/neurotransmitters of the brain. Epileptiform
discharges result in shift in the balance of brain excitatory and inhibitory processes due to different types of structural and/or functional alterations. The reverse is also equally true (Gulyás-Kovács et al, 2002). The histaminergic neurons are connected in many ways to both inhibitory and excitatory systems; e.g., they receive GABAergic input and have functional GABA_A receptors (Haas et al, 1991). Release of endogenous HA in rat hypothalamus can be suppressed by the excitatory amino acids glutamate or aspartate through N-methyl-D-aspartate (NMDA)-receptors (Okakura et al, 1992). The neuromodulator HA is believed to decrease the release of glutamate - an important excitatory neurotransmitter of the brain (Brown and Haas, 1999). Therefore during epilepsy which is a manifestation of the hyperexcitation of the neurons due to various possible reasons, there is decrement in the histamine level as is observed in the present study. Also intimate relationship has been proposed between histamine and GABA in modulation of convulsion. It is well known that GABA is the most important transmitter for inhibition of epilepsy in both humans and animals. Both GABA and histamine coexist in single neuronal cells of the posterior hypothalamus of rat (Takeda et al, 1984). Ericson et al (1991) also reported that neurons of the histaminergic tuberomammillary nucleus contain the neurotransmitter GABA. It has been reported that GABA mimetic drugs such as diazepam (Kamei et al, 1981), sodium valproate Albertson et al, 1980, and muscimol (Morimoto et al, 1987) are effective in inhibiting amygdaloid kindled seizures in rats.

It has also been found that simultaneous use of clobenpropit (a representative H_3 antagonist which stimulates HA release in histaminergic presynaptic terminals) and GABA mimetic drugs, which showed no significant change in effect when used separately, resulted in significant inhibition of amygdaloid kindled seizures (Ishizawa et al, 2000).

In addition, Soria-Jasso and Arias Montaño (1996) found that histamine stimulates
Again inhibition of amygdaloid kindled seizures induced by clobenpropit has been reported to be antagonized by bicuculline, a specific GABA<sub>A</sub> antagonist, whereas the effect of diazepam was not antagonized by the H<sub>1</sub> antagonist diphenylhydramine. These findings suggest that the potentiating effects of GABA mimetic drugs and clobenpropit may result not from the activation of the histaminergic system by GABA but from the activation of the GABAergic system by histamine (Ishizawa et al., 2000). Therefore it is reasonable to assume that CNS hyperexcitation during epilepsy at first excites the cerebral cortex which triggers increased HA release and consequently GABA release for combatting the excessive excitation. However, prolonged hyperexcitation and the hypersynchronization of the neuronal population results in negative feedback control of cortical hyperfunctionality by the cerebellum via the direct hypocerebellar histaminergic pathway (Shen et al., 2002). As a result there is significant decrement in regional brain HA level during epilepsy. Sato and Nakashima (1975) reported that whole brain norepinephrine and dopamine content were depleted in the hippocampus, midbrain, limbic lobe and cortex of amygdaloid kindled rats. On the other hand, Engel and Sharpless (1977) reported that a consistent and significant decrease in the level of both norepinephrine and dopamine was observed only in the stimulated amygdala of kindled rats. Watanabe et al (1984) demonstrated that both norepinephrine and histamine are biogenic amines which showed similar distribution profile in the rat brain. Therefore it seems likely that same idea is also applicable to the histamine.

It was further found in the present study that HA level did not change significantly in any of the brain areas 30 days after the last kindled as well as PCN induced seizure. The present study is essentially similar to that of Toyota et al (1998).
that no significant change was found in HA content one month after the last kindled seizure.

v) Modifications of the Nucleic Acid Pattern:

It is evident from the results of the present study that chronic epileptogenesis resulted in a fall in brain RNA and DNA. However in the acute epileptic animals there was increase in these nucleic acid levels. Studies in nerve cells opine that the amount of DNA and RNA and their pattern of aggregation depend towards the active state of the nerve cells (Weinstein, 1965). An increased production of RNA and DNA is accompanied with increased production of neuronal activity. Adequate stimulation for a short time may increase the concentration of both DNA and RNA, whereas prolonged or very intense stimulation may lead to a reversible decrease in both RNA and DNA. Large difference in the RNA and DNA of the individual neurons reflect difference in the functional state of the cell (Weinstein, 1965). The present results are in corroboration with other findings (Maiti et al, 1968) where marked decrease in RNA and DNA content were observed after prolonged treatment of cockroach ganglia with penicillin. Sarkar and Maiti (1968) also reported of increased functional activity of the isolated cockroach ganglion attained by PCN treatment is accompanied by increase in the RNA distribution while prolonged treatment decreased significantly the distribution pattern of the basophilic granules of the ganglion along with increase in the RNA distribution.

Numerous antibiotics, e.g. actinomycin, chloromyocin and oligomyocin have been reported to inhibit RNA synthesis in the mammalian cerebral cortex (Koenig, 1976). Although PCN is said to have no such action on mammalian brain, it is reported to inhibit specifically, the cellular dissimilation and RNA and DNA causing lysis of bacterial cell wall (Weinstein, 1965). The present study indicates such a possibility.
vii) Structural Modifications:

Histological studies have shown that penicillin applied intracortically provokes during first few weeks, a pattern of necrosis, oedema or scar around the epileptogenic focus. An infiltration of small cells and an increase in vacuolization is evident only after 15 days. Some inflammatory reactions surrounding the lesion could be found also. Sometimes the epileptogenic lesions were very widespread with multiple dissolute appearance of the piamater. More severe reactions around the chronic epileptic focus were found in those animals where penicillin was injected repeatedly and the animals were sacrificed after 30 days. Severe alterations were seen regarding the cell and nuclear size.

In the PTZ epileptic model not much cytological destruction was observed though the average cell and nuclear size had decreased to some extent. Also there were signs of microvacuolation and shrinkage of cell body.

In the amygdaloid kindled rats, the structural changes observed were much severe as compared to the controlled and PTZ epileptics. The neuron loss was marked (~50%) in the granule cells. Also there was swelling and vacuolization of cell bodies and dissolution of nucleus.

It is evident from the present study that both prolonged and brief seizures can cause neuronal loss. Seizure-induced neuronal loss may occur both acutely, as the result of an initial insult, and chronically, due to subsequent progressive injury. The extent of cell damage was much more in prolonged and recurrent seizures. Prolonged seizure activity was accompanied by neuronal loss, with seizure duration correlating to the degree of neuronal injury.
The results of the study clearly prove the long time belief (Townsend, 1976) that epilepsy is a disorder of the functional state of the brain which does not affect the brain structure, a myth. Indeed structural damages do accompany epilepsy. A cause-and-effect relationship between seizures and neuronal injury that accounts for epileptogenesis and chronic refractory epilepsy in humans is difficult to establish. In animal models, seizure duration or frequency can be controlled and the associated damage can be examined histologically. In humans, the effect of naturally occurring seizures on brain structure can only be examined postsurgically, postmortem, or through noninvasive imaging techniques. Animal models have shown that severe and/or frequent seizures can result in changes in neuronal structure and function that predispose animals to recurrent seizures. Although tantalizing to extrapolate these findings of seizure-induced epileptogenesis and neurobiologic changes to human epilepsy, certain epilepsies clearly do not fit with these observations, such as absence and benign rolandic epilepsy, in which epilepsy eventually remits despite frequent seizures. Nonetheless, animal models may provide insight into how some chronic, refractory epilepsies evolve.

Before closing:

The journey of neurotransmitters can be traced back to early 1900 when Elliot (1905) influenced by Langley’s experiments with adrenal gland extracts (Langley, 1901) advocated chemical messengers to be responsible for neuron-neuron communication. The earliest transmitters considered for central roles were acetylcholine and norepinephrine, largely because of their established roles in the somatic motor and autonomic nervous system. However it was only in the 1960s, serotonin, epinephrine and dopamine were identified as potential CNS transmitters (Bloom, 1996). Histochemical (Dahlstrom and Fuxe, 1964) as well as biochemical and
pharmacological data yielded results consistent with roles as neurotransmitters, but complete satisfaction of all criteria were not achieved until the 1970s (Brodie and Shore, 1957) till the identification of different antagonists (Curtis et al, 1971; Otsuka, 1973). From then on extensive studies have been carried out with the CNS transmitters. These transmitters sometimes singly often with cohorts have been found to have a cause-effect relationship with various neurodegenerative disorders like Parkinson’s disease, alzheimer’s disorder, epilepsy etc.

The history of epilepsy, one of the most common, serious neurological disorders, can easily be traced back to ancient times. In ancient Indian Ayurvedic literature of Charaka Samhita epilepsy is described as "apasmara" which means "loss of consciousness". Another ancient and detailed account of epilepsy is on a Babylonian tablet in the British Museum in London dating as far back as 2000BC. The tablet accurately records many of the different seizure types we recognize today. The Babylonian view was the forerunner of the Greek concept of "the sacred disease", as described in the famous treatise by Hippocrates (dated to the 5th Century BC).

While both Hippocrates and the Charaka Samhita provided less spiritualized understanding, the perception that epilepsy was a brain disorder did not begin to take root until the 18th and 19th Centuries AD. The intervening 2,000 years were dominated by more supernatural views. The modern understanding of the disease only began in the middle of the 19th century—1865 onwards to be precise (Friedlander, 2001).

In 1873 Hughlin Jackson presented his famous definition of epileptic seizures as ‘occasional, sudden, excessive, rapid and local discharges of grey matter’. This new definition ended all the previous misconceptions about the condition - a person with
epilepsy was no longer possessed by the devil neither was epilepsy now regarded as being contagious.

In the years to follow progresses were made in leaps and bounds to explore the vistas of biochemical base of epilepsy. The search is still not complete as on 2003. This job becomes more challenging as epilepsy is not a single disease but multifactorial disorder. The clinical condition of epilepsy can be replicated in experimental situations by different chemical, electrical or surgical procedures. Clinical epilepsy can result from diverse causes. Symptomatic epilepsy results from a known condition or injury producing spontaneous recurrent seizures in previously normal brain. However in many the raison d'être remain unidentified and such epilepsies are grouped as idiopathic.

It is universally accepted over the years that a great variety of human disorders including several dysfunctions result from body's unconscious reaction to physiological homeostasis jeopardy. This is characterized by internal self monitoring auto-regulatory mechanisms subjected to several homeostatic regulatory controls.

An imbalance of such control mechanisms occurring during long term repeated reactions develop disturbed persistent maladjustments and are reflected in several neurodegenerative dysfunctions including epilepsy – predominantly a chronic disorder. This is the biochemical basis of epilepsy. Some of the neurotransmitters are often linked to the disorder. As has been observed in this study, seizure activity is found to be associated with a wide range of local biochemical changes, affecting various neurotransmitters viz. NE, DA, 5-HT, HA. Similar changes have been observed by other researchers in different models of epilepsy. NE and 5-HT depletion have been shown to facilitate development of seizures in rats (Corcoran and Mason, 1980; Cavalheiro et al, 1981; Bortolotto and Cavalheiro, 1986) again Kokaia et al (1989) reported of increased NE in hippocampus of kindled rats. Decrease in HA content following
epileptogenesis have also been reported in various reports (Toyota et al, 1998; Yokoyama et al, 1996). Such differences in the neurotransmitter changes are either due to alterations in the transmitter synthesis and/or its metabolism. A marked increase in DA and 5-HT metabolites has been observed (Sperk et al, 1983), suggesting an increase in the firing rate of monoaminergic neurons immediately after systemic kainic acid (KA) injection (Arias et al, 1990). Noradrenaline system is believed to respond to epileptic seizures by increased transmitter release after kindling (Kokaia et al, 1989). In addition to possibly altering catecholamine concentrations in particular brain regions, epileptogenesis could alter catecholamine systems by changing the release and/or uptake mechanisms for the transmitter (Kant et al, 1980). The present study clearly indicates the importance of monoamines in the different epileptic phenomena.

Comments

It has been known since decades that great variety of diseases may result from the unconscious reaction of the body to physiological stress and vice versa. Epilepsy itself is stressful and fear of having seizures may provide the situation to bring about exactly that which is feared. Dr. Timm Betts, in his article 'Epilepsy and stress' (1992) wrote: "Although epilepsy may take place in the brain it may profoundly influence the morale, well being ...... may briefly change the way a person thinks, feels and acts- but how a person thinks, feels and acts may also change his or her epilepsy" (Friedlander, 2001).

Epilepsy in general and experimental epilepsy as is seen here causes functional anhomeostasis stress and long term maladjustments reflect into altered physiological condition. Such anhomeostacy probably occurs due to modulation of different neurotransmitter synthesis and/or neurometabolic state. GABA and glutamate have been the two classical targets for antiepileptic drugs, our findings may well usher a
newer approach which needs to be taken into account during antiepileptic drug
development.

We would have got a more detailed picture could have we availed the facilities
of more sensitive and sophisticated techniques like microdyalysis, HPLC and electron
microscopic (EM) study. We could then well be able to measure neurotransmitter
contents in all the seizure phases-preictal, ictal and post ictal continuously. Such phase-
wise data would benefit in drug dosage determination for different stages of epilepsy.
EM study would have aided us in visualizing the ultra structural changes of the brain
tissues.