Chapter X

SUMMARY AND CONCLUSION

The present study was performed to investigate the relation between epilepsy and brain neurotransmitters. For investigation of this study, the following different objectives were taken under consideration.

1. Quantitative analysis of monoamines (norepinephrine, dopamine, serotonin and histamine) in different brain areas of experimental epileptic rats as compared to control rats.

2. Nucleic acid fragmentation is a marker for neuronal injury. Therefore study was also undertaken to see whether experimental epilepsy produced any fragmentation of RNA and DNA.

3. A critical analysis of behaviour pattern and EEG recordings in control and experimental epileptic rats.

4. A detailed understanding of the histomorphology, cell structure, cell volume, nuclear volume and fibre connections of different brain areas in normal and in experimental animals following identical induction of epileptogenesis.

Experiments were performed on rats experimentally made epileptic with intracortical PCN injection, intraperitoneal PTZ application and kindling of the basolateral nucleus of amygdala.

For preparation of chronic penicillin epileptic animals PCN (100 IU, 100μl) was given thrice in the somatosensory cortex of each rat. However, for acute animal preparation penicillin was administered only once.

PTZ was administered at a dose of 20mg/kg in each rat for preparation of acute epileptic models.
For chronic amygdaloid kindled rats, stimulation (200-350 μA, 0.5msec, 60 Hz, 1-2 sec duration) was given in the basolateral nucleus of amygdala.

Following induction of epileptogenesis, behavioural and EEG changes were noted at first. Next the animals were sacrificed and the monoaminergic and histomorphological studies were carried out in the experimental and control groups. Nucleic acid fragmentation was also noted. The observations may be summarized as follows:

1. PCN and PTZ administration in the rats resulted in immediate onset of seizure predisposition followed by generalized convulsion and tremor. These behavioural manifestations appeared similar to human generalized and myoclonic (absence petitmal) epilepsy respectively. Amygdaloid kindling in rats did not result in immediate onset of seizure. Generalized seizure was observed only in the fully kindled rats though behavioural manifestations like head nodding and facial and limb clonus were observed throughout the kindling development period.

2. All the animals made experimentally epileptic developed epileptic EEG activity. PCN induced epileptogenesis was marked with irregular, spike-wave discharges, while PTZ epileptogenesis was marked with spikes, waves and domes. In the amygdaloid kindling rats a progressive development of after discharge was observed.

3. The long time belief that epilepsy is a disorder not of structure but of function has been proved to be a myth in this present work which clearly demonstrates that sudden and recurrent abnormal functioning of the brain cells does result in structural damage.
4. Changes in NE level were observed after induction of epileptogenesis. During PCN induced acute and chronic seizure predisposition level of NE was found to be lowered in the cerebellum, midbrain and caudate nuclei. However a higher NE concentration was observed in the cerebral cortex of the 15 days chronic PCN case. In the acute PCN and 15 and 30 days amygdaloid kindling models NE level had decreased. NE level had increased in the cerebral cortex of the PTZ treated group. However the same had decreased in the other areas.

5. Alterations in DA concentration were observed in our study after induction of epileptogenesis. Penicillin significantly increased DA level in the cerebral cortex and midbrain but decreased in the cerebellum and caudate nucleus. In the kindled group, 15 days after amygdaloid kindling a significant enhancement in the DA level was observed in the cerebral cortex, however, no comparable change in concentration of the neurotransmitter was observed in the cerebellum, caudate nuclei and the midbrain. 30 days after the last kindled seizure DA level in all the areas were normal. In the PTZ treated group also DA level had increased significantly in the cerebral cortex and midbrain though the level had decreased in the cerebellum and caudate nucleus.

6. Upon penicillin induced epileptogenesis, 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. 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.
7. The brain HA level was also found to be altered during epileptogenesis. A decrease in HA level was observed in the cerebellum, midbrain and caudate nuclei, and an increase in the cerebral cortex in the 15 days PCN group. 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. 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.

8. It was also long believed that nucleic acid pattern alterations are associated only with genetically epilepsy prone subjects. But the present study shows that the nucleic acid level does get lower in chronic epileptic conditions although the level shoots up after the initial insult.

The results thus reflect upon a direct relation between seizure predisposition and alterations of the brain neurotransmitters and the observations support our concept that noradrenergic and/or 5-hydroxytryptaminergic and/or dopaminergic and/or histaminergic abnormalities are etiologically important in seizure susceptibility in these models.

In conclusion, the present investigation suggests that abnormalities in specific neurotransmitter system play important role in epilepsy. Seizure activity is associated with wide range of local biochemical changes affecting various monoamines such as NE, DA, 5-HT and HA. These specific neurotransmitters take an active part in the control of brain activity. There may be a release of excitatory and inhibitory transmitters into the brain regions in response to nerve signals. The excitation passes down the cortex to widespread areas of brain and excites all the neurotransmitter systems.
differentially causing liberation of the neurotransmitters at different terminals which maintain the normal integrity of the brain functioning.

Hence our study supports the idea that epilepsy jeopardizes the normal monoamine equilibrium of the body which causes an imbalance between the excitatory and the inhibitory systems which are triggered differentially.

This study of neurotransmitter systems in these three epileptic models has given a glimpse of a therapeutic approach for epilepsy, which may be beneficially used during antiepileptic drug developments in contrast to classical GABA and glutamate modulating approaches.

Before closing the present chapter we open up some avenues for future investigations:

1. The neurotransmitter content in other areas of CNS as well as in the serum has not been measured during these experimental conditions.
2. The neurotransmitter output measurements would reveal a clearer picture.
3. Observations upon administration of these neurotransmitters iontophoretically into the body would further substantiate our results.
4. This study can be expanded, diversified by replicating in other experimental epileptic models analogous to human epileptic conditions.