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Current Topics in Epilepsy

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Abstract

Human epilepsies, by definition, are recurrent, self-sustained, paroxysmal disorders of brain function characterised by excessive firing of cerebral neurones. The underlying biochemical and morphological disturbances in the brain which are responsible for epilepsy are not clearly understood except that they appear to be diverse and hence the immediate difficulty in advancing a common mechanism for these disorders. Most probably they are different diseases but the clinical manifestations of these are similar. This view would certainly be compatible with the complex nature of neuronal control mechanisms both at the cellular and organisational level. In this article there will be a stress on possible biochemical disorders both in humans and in experimental epilepsies, the drug treatment of these, and an evaluation of the clinical relevance of experimental animal models.

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Research

It is a sobering thought that we are scarcely any more advanced in our concepts than were Jackson and his contemporaries. Our knowledge is more detailed, diagnosis of cerebral lesions is more reliable, the techniques of neurosurgery are immeasurably improved, but we still know very little about how to treat Idiopathic Epilepsy. The difficulty lies in the nature of the disease, fits occur at unpredictable intervals. All attempts to produce a reliable test for epilepsy have failed, and hence all measurements of the effects of drugs must be based on statistical techniques. The use of laboratory animals in whom epileptogenic are induced can provide material but computer techniques must be used to make the very large numbers of measurements needed to obtain statistically significant results.

The Patient

With all the statistics, the computers, and the drama of Neurosurgery we must not forget the individual for whom all this work is being carried out. The patient, as I said at the start, suffers not from Fits but from Fear. His own fear that he may suffer a convulsion at a dangerous or socially

embarrassing moment. The fears of his parents and his friends, of his employer and of society at large. It is an open question whether the truculence of the "epileptic personality" is a result of any specific organic lesion or merely a response to the intolerable pressures of "living with fits". Education can help Society to loose its irrational fears. Psychiatrists and Social Workers can offer support. The Doctor's role is to try and find and treat the cause, but most important of all, to help the patient to plan his life with realism and to live it with confidence.

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CURRENT TOPICS IN EPILEPSY

IAN TULLOCH

Introduction

Human epilepsies, by definition, are recurrent, self-sustained, paroxysmal disorders of brain function characterised by excessive firing of cerebral neurones. The underlying biochemical and morphological disturbances in the brain which are responsible for epilepsy are not clearly understood except that they appear to be diverse and hence the immediate difficulty in advancing a common mechanism for these disorders. Most probably they are different diseases but the clinical manifestations of these are similar. This view would certainly be compatible with the complex nature of neuronal control mechanisms both at the cellular and organisational level. In this article there will be a stress on possible biochemical disorders both in humans and in experimental epilepsies, the drug treatment of these, and an evaluation of the clinical relevance of experimental animal models.

Many cases of epilepsy are idiopathic, in that no underlying lesion can be found in the brain. This has led to the view that everybody has a threshold for epilepsy and it is this which determines whether or not seizures may develop. Genetic make-up seems to be important in some cases, especially gene-dependent errors of metabolism which are inherited as autosomal recessives, such as phenylketonuria, which results in accumulation of products of phenylalanine, and this is often accompanied by convulsions but the cause-effect mechanism is unknown. Numerically, however, these particular diseases are rare. *Conrad* (1935-38) did a study of twins with idiopathic and symptomatic epilepsy. He studied monozygotic and dizygotic twins and his results showed that 19 out of 22 of the monozygotic twin pairs were concordant with regard to epilepsy, and in 127 dizygotic pairs there was concordance only in approximately 4%. His studies were an attempt at measuring the correlations between a given genetic make-up, and brain electrical activity as measured by the EEG; he concluded that heredity did have a determining role in epilepsy which was idiopathic in nature. Symptomatic epilepsy, i.e. where there is a known lesion, was also included and heredity only played a minor part in this syndrome.

Refsum (1972) proposed a hypothesis of a polygenic influence being important in a predisposition to epilepsy and this interplays with various environmental precipitating factors.

Classes of epilepsy

Epilepsy can be divided into two main groups:

(a) *Focal epilepsy*

In many areas of the brain localised lesions can cause focal epilepsy. Usually the hyperactive neurones are localised in or around the lesion area. Lesions can be caused at birth, after head injury or more obviously by a tumour. These lesioned areas exhibit abnormal firing as shown by the EEG. The temporal lobe is particular susceptible to lesions and much interest has been shown in this type of epilepsy.

(b) *Generalised Epilepsies*

Petit mal and grand mal come under this heading and are characterised by abnormal electrical activity in large areas of brain rather than in a focal area. These are the more serious types of epilepsy since they result in loss of consciousness and severe seizures may occur. Petit mal is a very characteristic type of epilepsy in which there is a sudden complete loss of consciousness lasting for a few seconds followed by a sudden and complete return to normality. Grand mal is only diagnosed when unconsciousness and convulsions are known to have occurred. An important point here is that focal epilepsy can progress to a grand mal seizure, but grand mal seizures frequently occur independently of focal epilepsy.

These epilepsies are the main ones, but there are many others which have different clinical manifestations.

Neurochemistry of Epilepsy

(a) *Problems*

Biochemical research into epilepsy is greatly restricted by the difficulty in obtaining human biopsy and autopsy material. A study of a particular lesioned area from the brain may not reveal much concerning the initial cause of the epilepsy since the tissue that is actually epileptic may only be a small part of the sample or the tissue may be gliosed and neurones may be degenerated. *Pope* has proposed that the actual epileptic area is on the periphery of the lesion and

perhaps more emphasis should be placed on studies of this region.

This difficulty in obtaining neural tissue and the need for screening tests for anti-epileptic drugs has necessitated the use of experimental animal models. These models should ideally show similar behavioural and electrical manifestations to the particular type of human epilepsy under investigation. Many experimental models are now in use for different types of epilepsy, and this allows for a detailed biochemical and histological analysis of the brain. A detailed description of all models is not presented but only the most useful ones.

(a) *Animal Models*

(1) *Focal epilepsy*

Included in these are the topical convulsant metals, e.g. cobalt and alumina cream. These agents can be used to produce localised lesions in the brain but degeneration can be quite widespread as has been shown by histological study of the cobalt metal. Cellular destruction occurs at the lesion site and makes biochemical analysis of the tissue difficult and so many studies have investigated the secondary focus. Briefly, this is a focus which is homotopic to the original focus, if cortical in position, and has the advantage that it is an epileptic focus not accompanied by gross cellular destruction.

Drugs are tested for their ability to prevent focal discharge or to prevent seizure propagation and part of the clinical relevance of the model can be evaluated from these studies. Increasingly, more workers are doing biochemical studies on experimental models and trying to relate these to the human situation. For example, the recent work of van Gelder showed that in freshly excised cortical tissue from focal epileptogenic lesions in man there was a fall in glutamic acid, GABA, taurine and a significant rise in glycine in the area of the active focus. These amino acids are thought to have a transmitter function in the CNS and a change in their levels may indicate an imbalance between excitatory and inhibitory mechanisms. In a parallel study by Koyama on cobalt focal epileptogenic lesions in the cat, significant and very similar changes in transmitter levels were observed in the actively discharging focus.

An advantage of an animal model is that the development of epilepsy can be studied and Koyama was able to show that the fall in glutamic acid as measured in the

tissue was paralleled with an increased release of free glutamic acid from the cortical surface and the fall in GABA was a later development. Perhaps the initial release of glutamic acid, a postulated excitatory CNS transmitter, might be responsible for the development of a pool of hyperactive neurones. The fall in GABA, probably an inhibitor transmitter, is probably a result of a decrease in its precursor glutamic acid but it may be an important biochemical change with regard to the chronic nature of the experimental model.

Cation levels, intracellular and extracellular, are very important for neurone stability. The enzyme Na-K ATPase is membrane bound and requires ATP to transport Na^+ and K^+ ions across the neuronal membrane. Another important function of this enzyme is the re-uptake of transmitters into nerve endings, a mechanism which is very important in the inactivation of transmitter action on the post-synaptic receptor. Impairment of activity in this enzyme system might result in changes in ionic gradients and in alterations in transmitter release and re-uptake.

Hunt and Craig in a recent study on the cobalt model in rats, investigate cation levels and Na⁺-K ATPase activity in brain during the development of epilepsy. Their results were indicative of a change in ion transport since they reported an increase in Ca^+ , Na^+ , Mg^{++} and a fall in K^+ , Na-K ATPase and protein content in the area of the lesion. No significant changes were detected in the secondary focus of epileptogenic activity.

(2) *Generalised Epilepsies*

I. *Grand Mal*

Two models are most commonly used in the evaluation of drugs effective in grand mal:

(i) The Maximal Electroshock Seizure (MES) pattern test.

This is a relatively crude test that involves measurement of the dose of a drug that abolishes the tonic extensor component of the seizure induced by supra-maximal stimulation of the brain in 50% of all animals. Basically it is a measure of the drug's ability to prevent propagation of the epileptic discharge through brain tissue, and it is valuable since all drugs that have anti-grand mal activity in man are effective in the MES test in animals. Drugs that are

effective in cases of grand mal were discovered by empirical screening in various animal models, particularly the MES technique and the literature is lacking in detailed information on the mechanisms of drug action.

(ii) A possible action of anti-grand mal drugs is an inhibition of post-tetanic potentiation. Briefly, this is an enhancement of release of transmitter/volley for periods lasting up to several minutes after stimulating a nerve cell at a high frequency. A model frequently used is:

Recording the Mono-synaptic reflex in the spinal cord. After tetanic stimulation at the dorsal root for a minute has ceased, the amplitude of the mono-synaptic reflex increases. This increase can be almost completely blocked by diphenylhydantoin, a drug which is used extensively in chronic treatment of grand mal.

II. *Petit Mal*

The models for petit mal are not so well developed or tested as the grand mal models but a few models are useful. Systemic administration of pentylenetetrazol induces seizures which are decreased by anti-petit mal drugs such as ethosuximide. This model is poorly understood, especially since there are conflicting reports on what the action of pentylenetetrazole is.

These and many other experimental models have been used to study transmitters and energy metabolism in the CNS and a good deal of information is available relating to possible causal mechanisms for epilepsy. Manipulation of central transmitter levels by various methods has implicated all the known central transmitters in experimental epilepsy, but at the clinical trial level, as well as in experimental models, disappointing results have been obtained by attempts to treat epilepsy by altering specific transmitter levels in a known manner. This is perhaps forwarding a rather bleak picture concerning the rational treatment of epilepsy, but a certain degree of success has been obtained.

A notable example is the amino acid, GABA, for which there is good evidence from release, uptake, localisation and iontophoretic studies that it is an inhibitory transmitter in the CNS and at the neuromuscular junction in the crayfish. Glutamic acid is the precursor of GABA and the enzyme responsible for the catalysis is glutamate decarboxylase which requires vitamin B₆ as a co-factor. An important point is that the co-factor is weakly bound and, therefore, the enzyme is very susceptible to a vitamin B₆ deficiency or B₆

anti-metabolites. B₆ deficiency is not responsible for many cases of epilepsy but at least this evidence links a specific transmitter with a known cause of epilepsy, i.e. vitamin B₆ deficiency. This disease is probably due to some genetic abnormality.

Recent work on taurine, a possible neurotransmitter has shown that this amino acid prevents epilepsy in cobalt induced epilepsy in the cat and mouse, and van Gelder found a decrease in taurine levels in human focal epilepsy in the region of the focus. Physiological data indicate that iontophoretically applied taurine depresses activity in Renshaw cells, spinal interneurons and cerebral cortex cells which is strongly indicative of an inhibitory neurotransmitter function. Taurine is being used in clinical trials but no results are available as yet.

Changes in glutamate and GABA could possibly be *due* to a fault in the brain energy metabolism. The GABA shunt pathway provides an alternative route to part of the TCA cycle which is the chief energy generating system in oxidative metabolism. If some form of metabolic uncoupling is possible between the TCA cycle and the GABA shunt this could result in a change of GABA and glutamate levels. Alternatively the TCA cycle may not be properly functioning in cells and this could have the effect as previously mentioned as well as causing an ATP deficiency which may in itself be responsible for epilepsy. Certainly many experiments using metabolic poisons, e.g. cyanide, ouabain, have shown that convulsions are produced by these agents but the exact mechanism responsible for epileptic discharge of a cell is debatable.

An essential requirement for proper brain cell function is the maintenance of ionic gradients across neuronal and glial membranes and hence correct polarisation, e.g. high Na⁺ concentration extracellularly and low intracellularly in the normal state. The stress is on ion distribution rather than absolute amounts and research into this is limited because of the difficulty in the measurement of these gradients. Research into transmitter involvement in epilepsy is also complicated by compartmentation of these into metabolic and functional, i.e. neurotransmitter pools.

Clinical Aspects

Although changes in neurotransmitters, energy metabolism and ions have been implicated in experimental and human epilepsy, it is quite disappointing that so few new forms of successful

treatment have emerged. Although newer drugs are available, some of the drugs of choice are virtually unchanging and perhaps the major reason for this is that the new drugs are no real improvement on existing, well-tried drugs. Attention has recently centred on the correct plasma concentrations of anti-epileptic drugs and Marselli et al. have drawn attention to the lack of correlation between oral dose of diphenylhydantoin and plasma concentration in human patients. The main reasons for this are the differences between individuals in the rate of metabolism of drugs.

Adverse side effects are a major feature of the use of anti-epileptics since they are not specifically acting on epileptic cells but on normal cells as well. This is probably a major determining factor in the use of a given drug. A study by Gibberd throws light on the importance of clinical supervision over patients in their abilities to follow given dosage instructions. The reason for this may be that the side effects of the drugs are less tolerable than the actual epilepsy and this is clearly evidence for improvement in drug therapy. Correct plasma concentrations of anti-epileptic drugs are very important for them to be effective and also to reduce the side-effects.

Newer drugs are emerging for the treatment of some forms of epilepsy. The drug Diazepam, which is a benzodiazepine tranquilliser, has been found to be very effective in the treatment of status epilepticus in both adults and children and carbamazepine which is closely related to imipramine chemically, is effective in grand mal and temporal lobe epilepsy.

Concluding Remarks

Diphenylhydantoin and phenobarbitone are given on a chronic basis to epileptics and studies using animal models have rarely investigated chronic drug effects. Empiric screening of drugs in a battery of animal models has the disadvantage that it does not necessarily single out drugs that could be effective on a chronic basis. Onset of human epilepsy, especially after head injury, can occur and it would be very helpful if this could be prevented, possibly by administration of an anti-epileptic drug immediately after the injury. 80% of epileptics are treated by drugs and many of these are helped a great deal. However, there is a need to specify the modes of action of the anti-epileptic drugs and to develop drugs which are more specific to the disease.

In order to find out at first hand about this disabling condition, Res Medica went to see Mr James Glover, who for several years has been suffering from petit mal epilepsy. He told us about his condition:

"My first inclination on taking these turns came with sick tremors in my stomach. They then developed into the tremor followed by a black-out lasting a few minutes. This can happen anywhere, any time. It is like losing my memory. If I am talking I completely change the subject I am discussing. When the turn is over I return to where I was with the original conversation.

This started after a fall from a 20ft scaffold. I was sent to hospital and had an E.E.G. for the top half of my brain: no damage was found. This was twelve years ago. They associated it with my having tubercular meningitis when I was 19 years old. I was put on various drugs over the years without much success. Last year my doctor and I agreed that I should try the Andrew Duncan Clinic in Edinburgh to see if the illness was psychological. When I was having my last talk with the doctor I took one of these turns. The doctor made arrangements for me to have a lower E.E.G. done. This determined that my brain is damaged and an operation could cure me.

My experience with petit mal is one of frustration and annoyance. It has affected my working life. I am an electrical engineer and when I first took these turns was working with the transmission section of S.S.E.B. My work involved heights and high voltage electricity, also driving. I

was retired from S.S.E.B. on the grounds that I was a risk.

I am now in charge of maintenance at the Roxburghe Hotel, Edinburgh, and have worked there for three years handling all types of electrical and mechanical maintenance. My work is regarded as very satisfactory.

My home and social life is normal except for my complete impotence on which I blame these turns.

I am chairman of two committees for handicapped children: one is a parents' committee, the other is a rebuilding fund for the first secondary school for these children. I have proved that the latter will work and is worthwhile for the children's education and confidence.

My own little girl is slightly retarded and when I discovered this I blamed myself for her condition. When I found out that my wife was pregnant again I wanted the birth terminated. However, the doctor advised against it, and I thank God as everything has turned out fine.

The effects of this illness cause great embarrassment when in company as I not only do rather stupid things but sometimes can lose control of my bladder, and having to explain the situation to strangers is rather awkward.

I have now been assured by my neurologist that an operation is definitely possible and may be carried out in the very near future. This will be a very happy day for me as it should mean a return to normal life and I can now set my sights higher as these turns have held me back enormously regarding promotion."

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