CHAPTER 4
Epileptogenesis: Biochemical Aspects
B. Jarrott

A. Introduction
Epilepsies are defined as disorders of neuronal excitability characterized by periodic and unpredictable occurrences of seizures, while “seizures” are defined as transient changes of behaviour due to the disordered, synchronous, and rhythmic firing of populations of central nervous system neurons (McNamara 1994). These disorders of neuronal excitability can remain local or spread to other sites or engage all cortical regions simultaneously. Epileptogenesis could be defined as the molecular or cellular events producing the transient, disordered firing of a subpopulation of neurons in a key region of the brain, resulting in periodic seizures. A widely held view is that these seizures are caused by an abnormality in the major neurotransmitter systems of the brain such as excessive activity of the excitatory transmitters or impaired activity of the inhibitory transmitters, or a combination of both. However, the marked heterogeneity of syndromes (up to 50) diagnosed as epilepsy makes it most unlikely that there is a singular biochemical disorder that results in epileptogenesis. Furthermore, seizures set in motion a cascade of complex molecular and genomic changes, including changes in gene expression, sprouting of fibres, establishment of new synaptic contacts, alterations in expression of transmitters, modification of receptor expression, etc., that may contribute to the abnormally increased neuronal excitability and be responsible for a seizure-induced neuronal lesion. It is also recognized that epilepsy is an ongoing process in which repeated seizures may have an important impact on the brain and on the progression of the disorder. Thus it is essential that research should focus on understanding the biochemical basis of epileptogenesis since this should lead to the rational design of drugs both to prevent the development of epilepsy after insults such as head injury, brain tumours or febrile seizures, and also to minimize hyperexcitability at an existing epileptogenic focus which may be the result of a genetic disorder.

B. Methods for Studying Epileptogenesis
I. In Humans
1. Imaging Techniques
Technologies such as positron emission tomography and magnetic resonance imaging have had a dramatic impact on the evaluation for surgery of patients
with intractable epilepsy and are now providing valuable insight into epileptogenesis through non-invasive, longitudinal studies (Jackson and Connolly 1996; Theodore 1996; Kuzniecky 1997). Neurotransmitter receptors and transmitters such as γ-aminobutyric acid and glutamate can now be imaged with satisfactory resolution in epileptic patients and compared to controls (see Sect. C.I.2).

2. Neurophysiological Studies on Cortical Slices Maintained In Vitro

The increasing use of surgery to resect neocortical tissue containing the epileptogenic foci of patients whose seizures are resistant to pharmacological management, has provided a means for studying the neurophysiological, anatomical and neurochemical alterations in fresh human tissue. Avoli and Williamson (1996) have comprehensively reviewed such published studies with human material. While the data are very interesting, these authors concluded that they have not yet revealed any definite cellular mechanism that may account for the expression of the epileptiform activity in situ. A major problem is access to control cortical slices from healthy subjects. Nevertheless such studies need to continue and to be guided by findings from studies of brain slices from animal models of epilepsy.

3. Microdialysis

The development of a combined microdialysis/depth electrode probe (‘dialtrode’) that can be stereotaxically implanted in the hippocampus of patients being investigated for their suitability for surgery has allowed chronic studies of transmitter efflux before, during and after seizures (During and Spencer 1993) and has given insight into the biochemical basis of epileptogenesis (see Sects. C.I.1, C.I.2)

II. Animal Models

Animal models of epilepsy have played a key role for many years in both the screening and the development of potential anticonvulsant drugs and, more recently, in understanding the cellular and molecular basis of epileptogenesis (see also Chap. 2). The advantage of animal models is that adequate numbers of animals for meaningful statistical analysis can be obtained whilst invasive techniques, paying due regard to animal ethics principles, can give much more insight into the biochemical basis of epileptogenesis. Although over 50 different animal models have been reported that cover the multitude of types of epilepsy (Fisher 1989), this chapter deals primarily with the following 3 models:

1. Kindling

Kindling is an animal model of complex partial seizures (Goddard et al. 1969), a common form of epilepsy in humans and one that is not well controlled by conventional anticonvulsant drugs. Kindling in rats is the process of repeated,