

Section I

Introduction

Chapter

1

Concept of Causation in Epilepsy

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In this introductory chapter, general considerations relating to the meaning of *causation* in epilepsy are outlined, making the point, perhaps obvious but nevertheless worth iteration, that although cause is a crucial aspect of all cases of epilepsy, conceptualising or establishing or even defining causation is not as simple as it first may appear. I will end also with a brief summary of the classification of the causes of epilepsy as used in this book emphasising the difficulties encountered in attempting any unitary scheme, and finally with a note on nosology.

Can we Detect all Causes of Epilepsy? Is a Listing of all Causes Still 'an Act of Supererogation'?

The first edition of this book, published in 2011, had as its first chapter a historical introduction in which the evolution of ideas about causation from Hughlings Jackson to Lennox was outlined [1]. As mentioned there, the great mid-twentieth century neurologist Samuel Kinnier Wilson in 1940 wrote that the listing of all causes of epilepsy would be an *act of supererogation*. This was undoubtedly true in 1940 when most cases of epilepsy were cryptogenic in nature and the diagnostic technologies we take for granted today were not available. We wrote in the previous edition that perhaps now, a listing of all causes of epilepsy might be within our grasp, but this was over-optimistic. There is no doubt that the identification of causal factors for epilepsy has made major advances in the last five decades, but there remain an obdurate number of cases in which cause is obscure (the cryptogenic epilepsies) and, although the true proportion of all epilepsies that have remained cryptogenic has not been the subject of recent study, one might guess it is around 30% (or more, depending on definition of 'cause' – see below). These present a challenge for future researchers.

In approaching this topic, it is worth considering the structural and the non-structural abnormalities of brain tissue separately. In the case of structural changes, the technological revolutions of CT scanning and MRI have had an enormous impact. Using these technologies, almost any macroscopic abnormality of brain structure which is more than a few millimetres in size can now be visualised in the living patient, an inconceivable concept in Wilson's time. Because of this we can now, with a degree of confidence, diagnose most of the structural lesions which might cause epilepsy, and advances in this area have been impressive – particularly in relation to cortical

dysplasia, inflammatory, vascular and tumoural causes. There is, however, one possible category of 'structural' change which currently eludes diagnosis: the apparently normal variations in cortical structure which although demonstrable by MRI are not recognised to be involved in the pathogenesis of epilepsy. One can envisage for instance that there are certain changes in sulcal or cortical patterns, assumed to be within normal limits on neuro-imaging, that are in fact the basis of epilepsy. Examples which have been the subject of study, but with inconclusive results, include a 'star shaped' frontal gyrus and changes in gyral thickness or depth. Which (if any) of these variants are pathogenic is not apparent because of the lack of any universally agreed catalogue of normal gyral patterns and shape. Brains vary in many ways, but it is not known which variations carry pathological signification. This is an area in which novel and often ingenious imaging post-processing methodologies have been employed, but the results have been uniformly disappointing.

In the cases of epilepsies with no gross structural change, there have also been impressive advances. A large number of biochemical abnormalities have been identified through the developments in molecular science and molecular genetics. Perhaps not surprisingly, these have demonstrated that epilepsy can be the result of disturbance of numerous different biochemical pathways. Much still remains to be learned in this regard and there can be no doubt there are many biochemical changes which have currently escaped detection. It seems likely that unidentified biochemical changes underlie many of the epilepsies currently labelled as cryptogenic. A related category of disorders which may be important in causing epilepsy are disorders of neural networks ('wiring') which do not have a gross structural or any obvious biochemical or genetic basis. How important system changes are in the causation of epilepsy is largely unknown and our conceptualisation of these also has fallen behind. It has become fashionable to study 'connectivity' by clinical imaging methodologies but it seems to me that approaching microscopic abnormalities by looking at macroscopic structure is unlikely to be fruitful, and advances in the understanding of networks seem more likely to come from molecular genetics and biology than from any form of structural or functional imaging.

The Importance of Fashion

Wilson was writing at the height of the eugenic fever that had swept many centres of European and American academic

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epileptology, although as Wilson himself perceptively noted: ‘*The influence of the factor (heredity) is persistently overvalued*’. This illustrates an important principle – that of the importance of *fashion* in science. Let no one think that the path of the advance of science is not littered with fashion-led false starts and with turnings that proved simply to be cul-de-sacs – and eugenics is a classic example. The direction taken by eugenics is an illustration of the related point that science is strongly influenced by contemporary societal beliefs and mores – in other words, science is relative, not morally neutral and certainly not objective.

This applies to today’s science as much as to that of the past, and the thought that today’s opinions are necessarily the most advanced is naïve. In the field of epilepsy causation, there have been numerous fashionable theories which have proved subsequently unimportant, for example, theories of auto-intoxication, psycho-analytical theories of causation, reflex theories and eugenics. Each may have a certain degree of validity but each was massively over-hyped with speculation presented as fact. The same errors may well apply today and in modern neuroscience there are several examples of such over-promotion. Ray Tallis labelled this tendency ‘neuromania’ and his book serves as a wise correction to much of what has been written in the field of functional neuroimaging and neuro-genetics [2].

Assigning ‘Cause’ in Epilepsy

Any book on the topic of the ‘causes of epilepsy’ must of course first understand the limitations of the concept of ‘cause’ and these are pointed out briefly here (and were discussed in more detail in the previous edition of this book). The complexities of assigning cause include the following considerations.

‘Cause’ in Epilepsy is Often Multifactorial

The cause of an epilepsy is often the result of several interacting factors. These can be genetic influences, acquired influences and provoking factors. In this situation, assignment to any single aetiology is to an extent arbitrary. One cause may be overwhelming or predominant in some cases, but in others several aetiologies may contribute significantly. In these situations, it is best to consider aetiologies as ‘causal factors’ (i.e. susceptibilities) rather than ‘causes’. The use of the statistic the *odds ratio* for any particular causal factor gives a weighting of its importance and is an appropriate way of conceptualising the extent of a causal influence. Thus, in the case of epilepsy due to open head injury, the head injury is associated with a high odds ratio – and it can be considered statistically likely that that ‘cause’ contributes a great deal to the development of epilepsy; whereas the development of epilepsy after a mild head injury, with a low odds ratio, can be considered not likely to contribute a major susceptibility. I will return to the question of genetic susceptibilities below.

Is There a Distinction to be Drawn Between Predisposing and Exciting Causes?

Since the nineteenth century (and earlier), a distinction has sometimes been drawn between a *predisposing* and an *exciting* cause. The analogy of gunpowder and the match has been used, in which the combustibility of gunpowder is the predisposing factor and the spark from the match the exciting cause. The use of the concept of the *seizure threshold* is a version of this idea. Predisposing causes are usually internal, and the exciting cause is sometimes internal and sometimes external to the individual. An example would be the person with IGE who only has seizures when sleep deprived. The IGE is the predisposing factor and the sleep-deprivation the exciting (triggering) cause. Although some claim that the IGE is the ‘cause’, in my view there is no logical reason why both IGE and sleep deprivation should not be equally considered as ‘causes’. This is mentioned further below in relation to the inclusion of a category of provoked epilepsies in the listing of causes.

The Distinction Between Cause and Mechanism

Hughlings Jackson, in the 1860s, made a distinction between a ‘remote’ cause and a ‘proximate’ cause (i.e. the cellular molecular mechanism of epileptogenesis in the cerebral cortex). For instance, if a cerebral haemorrhage results in a seizure, is the ‘cause’ of the seizure the haemorrhage itself or the excitatory cortical cellular changes due to the haemorrhage? To Jackson, the real ‘causes’ of epilepsy are the cellular changes. I agree, and one can see that the more these molecular events are understood, the less relevant it becomes to assign a remote factor as the cause.

Epilepsy is a Process: and the ‘Cause’ May Evolve Over Time

It is important to recognise that the cause of an epilepsy in any individual often changes over time – and that the numerous molecular changes that occur in epilepsy contribute to the mechanisms of epileptogenesis. In many symptomatic epilepsies, for example, there is a ‘latent’ period which can extend for months or even years (after head injury, for instance) between the acute insult and the onset of late seizures. A process must be underway during this period which eventually results in seizures, although the exact nature of this process is not known. Suggested mechanisms include changes in neuronal networks, synaptic formation, glial function, biochemical or cellular function, inflammation and neurogenesis. These almost certainly continue after the onset of epilepsy and as the epilepsy evolves, its molecular basis (the ‘cause’) also changes. This could explain for instance the ease of treatment of early epilepsy compared to that of chronic epilepsy, and such clinical phenomena as the evolution of EEG changes in the course of epilepsy and the development of new symptoms such as psychosis in chronic epilepsy.

The Concept of Genetic Causes

The greatest advances in the understanding of causation in epilepsy in the last decade have been in relation to the genetics of epilepsy. However, this is a complex topic for several reasons.

First, there are numerous types of genetic mechanisms and in epilepsy examples of the following are all encountered: missense, nonsense, null or splice-site mutations; deletions, large or small; inversions or duplications and other copy number variants; trisomies or ring chromosomes; homozygous or compound heterozygous mutations; mitochondrial as well as nuclear inheritance; X-inactivation; and mosaicism. Epilepsy may be caused by gain of function as well as loss of function mutations in some genes. The effects of some gene mutations or CNVs may be caused by their effect on the expression of other genes.

It is also notable that even apparently simple Mendelian phenotypes can be associated with more than one gene (there are at least 14 examples including: GEFS+ and Dravet syndrome), some individual genetic variants result in different phenotypes and most genes have more than one abnormal variant sometimes with phenotypic heterogeneity. Similarly, some copy number variations (deletions and duplications) overlap with those causing autism, learning disability or schizophrenia, and the epilepsy and neuropsychiatric effects may occur at different stages of development. Some genetic variants affect networks which seem to result in epilepsy (for instance synaptic transmission, synaptic vesicle production or release, and memory and learning networks) [3].

A further and often overlooked fact is that some genetic variants confer only a very small risk of epilepsy. These are best conceptualised as ‘susceptibility’ factors, but are often over-promoted as ‘causes’. The susceptibility may be modified by other genes (epistatic) or epigenetic and environmental factors. In this regard, it is useful to consider the analogy of height. In a recent genome-wide association study some 294 831 SNPs were found to be statistically associated with height, no single gene has any major effect and furthermore very strong environmental influences also contribute to height such as diet, milk intake, hormones, childhood deprivation and abuse. The situation in epilepsy may be similar although perhaps not so extreme, and this should not be surprising as a genetic variant with a marked tendency to cause epilepsy would have been subject to strong negative selection pressures. How many genes there are conferring small degrees of susceptibility is completely unknown. A further problem is that, too often in this field, an association is found not to be causal at all but simply a chance finding. The literature in genetics and medicine is littered with the carcasses of false-leads. The same applies to most aspects of human behaviour, and it does seem that the genetic influences on brain function particularly are a butchers-shop in this sense. It is likely that many idiopathic and cryptogenic cases are, like height, the end product of genetic, epistatic, epigenetic and environmental factors acting at different times, and the small effects of any individual gene are almost meaningless. Furthermore, as epilepsy has very much an age-dependent expression, it is also likely that cerebral development is a crucial factor and this is under the strong influence of time-dependent environmental as well as genetic factors – almost no research has been undertaken in this area.

Wang *et al.* [4] in a landmark review identified 693 genes associated with epilepsy on Online Mendelian Inheritance in Man (OMIM) database which can be divided into three (overlapping) categories.

84 ‘epilepsy genes’: these were the 84 genes associated with ‘pure’ epilepsy and conditions where epilepsy is a predominant or core feature, including 28 ion-channel genes, 25 enzyme or enzyme regulator genes, 12 transporter genes and 19 other (e.g. cell adhesion, membrane trafficking, signal transduction, etc.). These genes are associated with large effects (especially those in infantile cases) and so are truly ‘causal’. In some cases, the genetic variants account for only very rare familial cases within a syndrome in which the majority of cases have now known genetic bases (for instance CLCN2 and EFHC1 in childhood absence epilepsy) and some are in studies which have not been validated (so 84 genes is likely to be an over-estimate of the real figure). This figure also includes: 42 genes associated with the epileptic encephalopathies (of which at least 56 different types have been identified) and other severe epilepsy syndromes (see Table 1.2), 10 genes associated with progressive myoclonic epilepsies, and genes for infantile inborn errors of metabolism which present with epilepsy (pyridoxamine 3’-phosphate oxidase deficiency and pyridoxine-dependent epilepsy). There are 29 genes (Table 1.3), causing 23 phenotypes, of the ‘idiopathic epilepsies’ as defined in Table 1.1.

73 ‘neurodevelopment associated genes’: these genes associated with neurodevelopmental abnormalities and the epilepsy are usually associated with other clinical features, including in most cases intellectual disability which is sometimes severe, and also structural defects of the brain (which can be visualised by MRI). Most of the mutations in these genes have large effects and so are truly causal, but many are very rare. Some of these defects (schizencephaly is an example) can also result from environmental insults and in some the cause is not found.

536 ‘epilepsy-related genes’: these are the genes causing ‘inborn errors of metabolism’ and other diseases of which epilepsy is only one amongst other clinical features. In some the epilepsy is mild and inconsistent, and in others severe and invariable. In these conditions, the epilepsy is always associated with other clinical features, including in most cases intellectual disability which is sometimes severe, and also often systemic or dysmorphic features and in some cases structural defects of the brain. Some of the genes are also associated with other diseases which only cause epilepsy indirectly.

All the genetic defects having a marked effect (i.e. the Mendelian epilepsies) are rare, for the obvious reason that inherited conditions causing epilepsy would face strong reproductive disadvantage. Taken together, these account at a rough guess for less than 5% of all epilepsies (and probably less than 1%). Others causing severe epilepsies (for instance in the early epileptic encephalopathies) are most often *de novo* dominant mutations.

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Table 1.1 A classification of epilepsy based on aetiology

Main category	Subcategory	Some examples ¹
IDIOPATHIC EPILEPSY	Pure epilepsies in which there is no clear single gene defect and which are likely to have a complex epistatic, epigenetic or developmental origin	Idiopathic generalised epilepsy (and its subtypes, for instance: childhood absence epilepsy, juvenile myoclonic epilepsy, epilepsy with grand-mal seizures on awakening). Idiopathic partial epilepsies of childhood (and its subtypes for instance: benign Rolandic epilepsy, benign occipital lobe epilepsy).
SYMPTOMATIC EPILEPSY OF GENETIC OR DEVELOPMENTAL ORIGIN	Pure epilepsies due to single gene disorders	Autosomal dominant nocturnal frontal lobe epilepsy; benign familial neonatal convulsions; familial lateral temporal lobe epilepsy; genetic epilepsy with febrile seizures plus.
	Epileptic encephalopathies and severe epilepsy syndromes ³	Dravet syndrome; early infantile encephalopathies (and its various subtypes); early myoclonic encephalopathies, Landau–Kleffner syndrome (some cases) ² ; Lennox–Gastaut syndrome (some cases) ² ; West syndrome (some cases) ² .
	Epilepsies with a mitochondrial genetic basis (including defects of nuclear genes affecting mitochondrial function)	MEGDEL; Leigh syndrome; MELAS; MERRF; NARP; POLG-related syndromes; mitochondrial deletion disorders.
	Progressive myoclonic epilepsies	Dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; neuronal ceroid lipofuscinoses; sialidosis; Unverricht–Lundborg disease.
	Neurocutaneous syndromes	Neurofibromatosis; Sturge–Weber syndrome; tuberous sclerosis.
	Inborn errors of metabolism and other single gene disorders	Angelman syndrome; disorders of creatine metabolism; CGD; fatty acid oxidation syndromes; Glut1 deficiency; lysosomal disorders; Menkes’ disease; neuroacanthocytosis; organic acidurias; PCHD19 syndrome; peroxisomal disorders; porphyria; pyridoxine-dependent epilepsy; Rett syndrome; CDKL5 encephalopathy; urea cycle disorders; Wilson’s disease.
	Disorders of chromosome function and copy number variations	Down syndrome; fragile X syndrome; inverted duplicated chromosome 15; ring chromosome 20; ring chromosome 14 and other ring chromosomal disorders; Wolf–Hirschhorn syndrome; X128 dup syndrome.
	Developmental anomalies of cerebral structure ³	Agyria-pachygyria-band spectrum; agenesis of the corpus callosum; arachnoid cysts; focal cortical dysplasia; hemimegalencephy; tubulinopathies and mTOR pathway disorders; microcephaly; periventricular nodular heterotopia; polymicrogyria and schizencephaly.
SYMPTOMATIC EPILEPSY OF ACQUIRED ORIGIN	Hippocampal sclerosis	Sometimes divided into subtypes.
	Cerebral trauma	Open head injury; closed head injury; neurosurgery; non-accidental head injury in infants.
	Cerebral tumour	Glioma; ganglioglioma and hamartoma; DNET; hypothalamic hamartoma; meningioma; secondary tumours.
	Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis; parasitic disorders; tuberculosis; HIV.
	Cerebrovascular disorders	Arteriovenous malformation; cavernous haemangioma; cerebral haemorrhage; cerebral infarction.
	Cerebral immunological disorders	Autoantibody autoimmune encephalitic disorders; Rasmussen’s encephalitis; SLE and collagen vascular disorders.
	Degenerative and other neurological conditions	Alzheimer disease and other dementing disorders; eclampsia; multiple sclerosis and demyelinating disorders; hydrocephalus; posterior reversible encephalopathy syndrome; vaccination and immunisation.
	Perinatal and infantile causes	Neonatal seizures (various causes); cerebral palsy; post-vaccination.

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Table 1.1 (cont.)

Main category	Subcategory	Some examples ¹
PROVOKED EPILEPSY	Reflex epilepsies	Auditory-induced epilepsy; eating epilepsy; hot-water epilepsy; photosensitive epilepsies; reading epilepsy; reflex epilepsies associated with higher-level processing; startle-induced epilepsies.
	Provoking factors	Alcohol and toxin-induced seizures; drug-induced seizures; fever; menstrual cycle and catamenial epilepsy; metabolic and endocrine-induced seizures; sleep–wake cycle; stress.
CRYPTOGENIC EPILEPSY		

¹ This listing of examples is representative but not exhaustive.
² These epilepsy syndromes can also have acquired causes.
³ Although included here, many cases have no known cause and others are caused by external (environmental) insults.

Table 1.2 Seventy-one genes associated with early infantile epileptic encephalopathies

AARS, ALG13, ARHGEF9, ARV1, ARX, BRAT1, CACNA1A, CACNA2D2, CDKL5, CHD2, DOCK7, DNM1, EEF1A2, ERBB4, FLNA, FOXG1, FGF12, FRRS1L, GABRA1, GABRB1, GABRB3, GNAO1, GRIN2A, GRIN2B, GRIN2DB, GUF1, ITPA, HCN1, HDAC4, HNRNPU, HNRNP1, ISEC1, IQSEC2, ITPA, KCNA2, KCNB1, KCNQ2, KCNQ3, KCNT1, MAG12, MEFC2, MTOR, NECAP1, NEDD4L, NDP, NRXN1, PCDH19, PIGA, PLCB1, PTEN, QARS, SCN1A, SCN2A, SCN8A, SETBP1, SIK1, SLC1A2, SLC6A1, SLC12A5, SLC13A5, SLC25A12, SLC25A22, ST3GAL3, SPTAN1, ST3GAL3, STXBP1, SZT2, TBCID24, TCF4, UBA5, WWOX
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(Data partly based on Wang *et al.* 2017 [4] and McTague *et al.* 2016 [12])

Table 1.3 Twenty-nine genes in which mutations are associated with the Mendelian pure epilepsies.

ADRA2B, CACNA1H, CACNB4, CASR, CHRNA2, CHRN2, CLCN2, CNTN2, CPA6, DEPDC5, EFHC1, GABRG2, GABRA1, GABRB3, GABR, GAL, KCNT1, LGI11, PRRT, SLC12A5, SLC2A1, SLC6A1, STX1B, SCN2A, SCN8A, SCN1A, SCN9A, SCN1B, TBC1D24
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(Data partly based on Wang *et al.* 2017 [4])

A final point is that the tendency to hyperbole is very striking in this field. The journalist David Dobbs has published an interesting analysis of this [5], pointing out that in 2000, Francis Collins, the leader of the Human Genome Project, predicted that the genomic revolution could reduce cancer to zero and would make gene-tailored personalised medicine common by 2010. This has resulted in the expenditure of billions of dollars, but as Dobbs puts it the genome-wide studies are infected by MAGOTS (Many Assorted Genes of Tiny Significance) resulting in the identification of ‘a mass of barely significant genes explaining little’. The same MAGOTs are found in the epilepsy world, and yet are often touted as breakthroughs. If similar amounts of research money, time and talent had been spent on the environmental or developmental determinants of epilepsy, it is possible that advances of greater practical utility might have been made.

Is Epilepsy a Disease?

Before moving to consider the classification of causes, it is worth considering the question of whether epilepsy is a disease (or condition), or simply a symptom.

Defining an *epileptic seizure* is relatively easy – as it is a physio–chemical entity the nature of which has been extensively explored. However defining *epilepsy* is more difficult. Lennox in 1960 stated that fits are the symptoms, and the epilepsies are the

diseases, and that what makes epilepsy a ‘disease’ is the fact that it has a ‘cause’. This is the strictly medical model of disease, and the emphasis on cause avoids any circular arguments about definition. Even if some cases are considered idiopathic or cryptogenic, this does not mean that there is no cause, but simply that the cause has not been identified.

However as written elsewhere [6] ‘This medical model of disease though is just one side of the coin. The idea of ‘disease’ has much more extensive connotations, and this particularly applies to epilepsy’. Temkin called epilepsy ‘a paradigm of the suffering of both body and soul in disease’, and the social and cultural connotations of epilepsy can often be far more important than the occurrence of seizures. In other words, *being epileptic* is far more than just *having seizures*. There are impacts on social interactions, social relationships, marriage, domestic life, education and employment. There are issues of dependency and identity, self-esteem and self-confidence. These dominate the lives of many patients. Although based on the occurrence of seizures, these aspects transcend the seizures. Seizures may occur typically once every few months and last a few minutes, but ‘being epileptic’ is a permanent internal (existential) state of being, a psychic position, which persists sometimes years after the end of the seizures. There are few conditions in which the disconnect between the symptoms and the disease state is so massive.

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In this book, which is focused on ‘cause’, we take a strictly medical model, but draw attention to the wider connotations which should not be forgotten in routine practice.

An Aetiological Classification of Epilepsy

If it is accepted that the medical definition of epilepsy depends heavily on its cause, then a classification of epilepsy by cause would be a logical step. However, the difficulties in assigning cause, mentioned above, complicate the basis of any such classification and much more satisfactory is a ‘catalogue’ or a ‘listing’ of causal factors, and this is exactly the form that this book takes. We have listed the factors which are strongly causal, but do so in the recognition that such factors may be only one aspect of causation in individual cases.

We have categorised the known causes into groups which it is hoped can provide a useful framework for research and for clinical work (Table 1.1). In relation to the genetic causes, the grouping differs in significant ways from that proposed in the first edition of this book [7,8], reflecting the enormous advances in this field.

1 Idiopathic Epilepsy

These are defined as those epilepsies in which seizures are the only or main clinical feature and in which no cause has been identified but which have clinical features strongly suggestive of a predominant genetic or developmental cause (including epistatic or epigenetic mechanisms). This category includes the idiopathic generalised and partial epilepsy syndromes which account for a substantial proportion of all epilepsies. It seems very likely that epigenetic, epistatic, environmental and development factors are more important than the influence of any individual gene.

2 Symptomatic Epilepsies of Genetic or Developmental Origin

These are defined as those epilepsies in which there is a predominant identifiable genetic or developmental basis. This includes: the rare cases of pure epilepsy due to a single gene defect; also the epileptic encephalopathies, neurodevelopmental disorders and the genetic inborn errors of metabolism which are associated with cerebral pathological changes or other major systemic or neurological features (including learning disability) in addition to the epilepsy; and also the so-called epilepsy syndromes in which genetic defects have been discovered, although in some syndromes, the aetiology is more complex with some cases without the genetic defects and some cases where the predominant causal factors are acquired.

3 Symptomatic Epilepsies of Acquired Origin

These are defined as those epilepsies in which the predominant cause is an acquired lesion. The term includes those epilepsies due predominantly to external or environmental factors (e.g. toxins, drugs, head injury) as well as those due to internal pathologic processes which have no known major environmental component (e.g. tumours, neurodegenerative disorders, autoimmune disorders). The epilepsy may be the only manifestation of the condition or associated with other neurological or systemic disorders.

4 Provoked Epilepsy

These are defined as those epilepsies in which a specific and transient systemic or environmental factor is the predominant cause of the seizures. Some provoked epilepsies will also have a genetic basis and some an acquired basis in which case an individual might be included in the other category, but in many, no other cause can be identified.

5 Cryptogenic Epilepsy

These are defined as those epilepsies in which no cause has been identified but which have pathological or clinical features strongly suggestive of an underlying symptomatic cause.

The following additional points can also be made.

- (a) The major change from the classification used in the previous edition of this book is the creation of a new category of ‘Symptomatic epilepsies of genetic or developmental basis’. This reflects the major advances made in epilepsy genetics over the last decade. Into this category are put the cases of pure epilepsy due to single gene disorders (previously included in the idiopathic category) and also the creation of the new subcategories of epileptic encephalopathies and of mitochondrial genetic disorders. Also included in this category are the genetically determined neurodevelopmental disorders, inborn errors of metabolism and neurocutaneous syndromes which were previously included in the symptomatic category.
- (b) The category of provoked epilepsy has been criticised on various fronts [9]. However, the category is retained here as in my view *provoking factors* are as much a *cause* as any other. It is true that some cases have genetic and some identifiable symptomatic cases, but in many examples neither can be found. The categories of symptomatic epilepsy of acquired origin and of provoked epilepsy combined are thus roughly equivalent to the category of the ‘exciting causes’ of the 19th century neurologists.
- (c) The distinction between idiopathic and cryptogenic cases is one of degree, but has clinical utility (and has been in long usage) and helps differentiate two quite different clinical presentations. It must be admitted though that there is a significant grey area between these two core categories.
- (d) There are no divisions into focal or generalised epilepsy. It should be noted that this distinction (problematic as it is) does not map across the idiopathic versus symptomatic categorisation. Some symptomatic epilepsies are generalised and some idiopathic epilepsies are focal, and the dichotomy really has little utility when it comes to an aetiological classification.
- (e) This framework of course has inexact boundaries, as do all classification schemes. Not least is the fact that in a substantial number of cases, there are multiple causal factors and inclusion into a category based on the predominant factor is a potentially arbitrary decision. The classification also mixes proximate

(mechanistic) and remote categories and, as knowledge advances, the proximate categories may render the remote categories less significant. Finally, too, the classification does not take into account the fact that the influence of specific causal factors in an individual case can change over time.

- (f) The term *acute symptomatic seizures* (or *acute symptomatic epilepsy*) is one which has caused much confusion, and is worth a particular note here. The Epidemiology Commission of the International League Against Epilepsy defined an acute symptomatic seizure as *a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult* and lists criteria for these. This definition is poorly thought through, as it includes the early seizures due to massive brain injury (for instance in acute stroke or encephalitis) as well as provoked seizures which have no underlying brain pathology (for instance, due to metabolic disturbance, fever or toxic exposure). The two situations are completely distinct from all clinical and prognostic points of view, and should not be mixed up. The second problem relates to the extremely arbitrary nature of the criteria for inclusion. For these reasons, it is here suggested that the term is abandoned as essentially meaningless or if retained, to be used only to refer to provoked seizures with no underlying brain pathology [10].

A Note on Nosology

Nosology is important. A careful choice of words and clear thinking is needed if nosological categories are to be changed, as change can cause confusion particularly amongst

non-specialists (and also for instance in legal, administrative circles, and in guidelines and other protocols). In my view, therefore, change should be made only if there is a pressing reason to do so, and if the change is due to a change in conception and not simple unnecessary meddling. A change can also have other downsides and unintended consequences [11]. The replacement of the word *idiopathic* with *genetic* proposed in the recent ILAE classification of epilepsy is a prime example of this point, for to label something genetic will have for many people and in many cultures serious consequences (to family relations, marriage, self-esteem and so on). Thus, we favour using the word genetic to refer only to those epilepsies in which there is a single gene disorder or which have a very strong genetic cause. Any individually small genetic influence, such as might be found in cases of IGE or of idiopathic partial epilepsies, has no practical bearing in relation to genetic counselling nor any implications for clinical management and these epilepsies should not be called ‘genetic’. The worst effect of changing the name from idiopathic to genetic is not having the gene but having the label. In our chapters in this book, we therefore have retained the word idiopathic and not substituted this with the word genetic, contrary to the ILAE preference. The term idiopathic is well understood and well established, and is anyway more appropriate as no genetic cause has been found in the vast majority of idiopathic cases, and these epilepsies are much more likely to be the result of a complex mix of genetics, epigenetic and environmental influences. To label these as genetic seems regressive and unhelpful. Similarly to replace the time-honoured words *cryptogenic* with *unknown* and to remove the word *symptomatic* seems unnecessary and meddlesome, with no real purpose, and we have retained these here.

References

- Shorvon SD. Historical introduction: the causes of epilepsy in the pre-molecular era (1860–1960). In: Shorvon SD, Andermann F, Guerrini R (eds.) *The Causes of Epilepsy. Common and Uncommon Causes in Adults and Children*. Cambridge, Cambridge University Press 2011, pp. 1–20.
- Tallis R. *Aping Mankind: Neuromania, Darwinitis and the Misrepresentation of Humanity*. London, Acumen 2011.
- Johnson MR, Shkura K, Langley SR, et al. (2016) Systems genetics identifies a convergent gene network for cognition and neurodevelopmental disease. *Nat Neurosci* 19(2):223–32.
- Wang J, Lin ZJ, Liu L, et al. (2017) Epilepsy-associated genes. *Seizure* 44:11–20.
- Dobbs D. What Is Your DNA Worth? https://www.buzzfeed.com/daviddobbs/weighing-the-promises-of-big-genomics?utm_term=.cwD3pPG0w#.eyMpQ5Gya.
- Schmidt D, Shorvon S. *The End of Epilepsy* Oxford, Oxford University Press, 2016.
- Shorvon SD. (2011) The etiologic classification of epilepsy. *Epilepsia* 52(6):1052–7.
- Shorvon SD. The etiological classification of epilepsy. In: Shorvon SD, Andermann F, Guerrini R (eds.) *The Causes of Epilepsy. Common and Uncommon Causes in Adults and Children*. Cambridge, Cambridge University Press 2011, pp. 21–23.
- Engel J Jr. (2011) The etiologic classification of epilepsy. *Epilepsia* 52(6): 1195–7; discussion 1205–9.
- Shorvon S, Guerrini R. (2010) Acute symptomatic seizures—should we retain the term? *Epilepsia* 51(4): 722–3.
- Shorvon SD. (2013) New terminologies: the downsides. *Epilepsia* 54(6):1134.
- McTague A, Howell KB, Cross JH, et al. (2016) The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol* 15(3):304–16.

Section I

Introduction

Chapter

2

Epileptogenesis in Idiopathic Epilepsy

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Introduction

Epilepsy is a disease of the brain characterized by recurring unprovoked epileptic seizures which are caused by a transient disturbance of cortical neuronal activity. Approximately 3% of people are affected by epilepsy throughout their lifetime [1], more frequently during childhood or in older age. Numerous causes of sporadic or recurrent seizures include trauma, tumors, stroke, altered metabolic states, or inborn brain malformations. However, an estimated 40% of all epilepsy patients have recurrent unprovoked seizures without other obvious neurological abnormalities. Owing to the obscurity of the seizure genesis, these syndromes have been designated as “idiopathic” epilepsies, although the presumed genetic origin has lately led to an alternative usage of the term “genetic epilepsies”. Various studies within the last two decades have reported mutations associated with idiopathic epilepsy syndromes in genes encoding proteins which regulate neuronal excitability, such as ion channels, transporters, receptors or presynaptic molecules [2–4]. The number of identified mutations and affected genes has dramatically increased in recent years since next generation sequencing technologies have been broadly employed to analyze large internationally assembled cohorts of patients. Strikingly, these new data corroborated the initial findings that genes encoding proteins mediating neuronal excitation and synaptic transmission are the most prominent epilepsy-associated genes [4–21,138].

The first inherited ion-channel defects were identified in families with rare monogenic idiopathic epilepsy syndromes, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) or benign familial neonatal seizures (BFNS). Ion-channel mutations were also found in a few families with the idiopathic/genetic generalized epilepsies (IGE/GGE), comprising childhood and juvenile absence epilepsy (CAE, JAE), juvenile myoclonic epilepsy (JME), and epilepsy with grand mal seizures on awakening (EGMA). The latest studies identified a large and steadily increasing number of variants occurring *de novo* in patients with epileptic encephalopathies, severe epilepsy syndromes associated with developmental delay and refractory seizures in the affected children. Furthermore, defects in several of the ion-channel epilepsy genes have been shown to result in both benign and very severe epilepsy forms [4,5,11,13–16,22–24]. At the same time, several genes have emerged as predominant factors in the genetic architecture of specific epilepsy syndromes. For instance, it has been shown that mutations in the glutamate (NMDA) receptor subunit

gene *GRIN2A* account for about 7.5% of cases with partial epilepsies of childhood related to Rolandic epilepsy [20].

Among the non-ion-channel genes that have been associated with idiopathic epilepsies so far are the leucine-rich, glioma-inactivated 1 gene (*LGI1*), mutations of which cause autosomal dominant lateral temporal lobe epilepsy. Interestingly, an interaction of LGI-1 with glutamate (AMPA) receptors or K⁺ channels has been described (reviewed in [2]). Other examples of non-ion-channel genes include the X chromosomal gene *PCDH19* (encoding protocadherin which is important for the interneuronal connections in early development) as one of the most common causes of epileptic encephalopathy in females [25,26], and *CDKL5* coding for serine/threonine kinase cyclin-dependent kinase-like 5 linked to severe epileptic encephalopathy [27]. Furthermore, mutations in *CHD2* (chromodomain helicase DNA binding protein 2) have been linked to both epileptic encephalopathy and generalized, especially photosensitive epilepsy [28,29]. Meanwhile, *DEPDC5* had been established as the most important focal epilepsy gene, pointing to a role of mTOR pathway regulating cell growth and proliferation in epileptogenesis [19,30]. Genetic research has also indicated that metabolic changes can predispose to idiopathic epilepsies, as found for mutations in the glucose transporter GLUT1 responsible for transporting glucose as the most important energy source for the brain across the blood–brain barrier. Beside the classical GLUT1 deficiency syndrome, which presents a severe epileptic encephalopathy [31], GLUT1 mutations have also been associated with milder phenotypes including idiopathic generalized – mainly absence – epilepsy [32–34]. In addition, copy number variations of certain chromosomal regions have also been linked to common epilepsies, suggesting further involvement of non-ion-channel genes [3], but will not be discussed in detail here.

This chapter focuses on the most important characteristics of voltage- and ligand-gated ion channels, their role in determining neuronal excitability, and the impact of some reported mutations on epileptogenesis in idiopathic epilepsies. A section describing the importance of the thalamocortical loop and thalamic ion channels for the generation of generalized seizures is also included. We also briefly address the potential role of presynaptic proteins in epileptogenesis. The clinical phenotypes of the mentioned syndromes are described in other chapters. We would also like to point out that not all genes, variants, and mechanisms can be included in this kind of overview, not only because of space limitations, but also because it is written in highly dynamic and productive times for epilepsy genetics.

Basic Structure and Function of Ion Channels and their Relation to Neuronal Excitability

Ion channels are pore-forming proteins residing in the cell membrane which confer the electrical excitability to a neuron. They are specialized to selectively conduct different ions and have gates, which regulate their opening and closing under well-defined conditions. Two major classes of ion channels most relevant for epileptogenesis are (i) the voltage-gated channels, opening in response to changes in transmembrane voltage, and (ii) the ligand-gated channels (also known as ‘receptors’) controlled by specific ligands, such as neurotransmitters. Whereas voltage-gated channels are responsible for the generation and conduction of action potentials along the axon, ligand-gated channels mediate synaptic transmission and signal transduction from cell to cell.

Voltage-Gated Channels

Voltage-gated cation channels have pores selective for Na⁺, K⁺, or Ca²⁺ ions. They consist of a main, pore-forming α-subunit responsible for gating and permeation, and accessory subunits

(β, γ, or δ) which have modifying effects. The α-subunits of voltage-gated Na⁺ and Ca²⁺ channels have a tetrameric structure comprising four homologous domains (I–IV), each with six transmembrane segments (S1–S6), all encoded by a single gene (Fig. 2.1A). In contrast, voltage-gated K⁺ channels’ genes only encode one domain, which in order to acquire a similar structure to the Na⁺ channel assemble into homo- or heterotetramers (Fig. 2.1B). The three major conformational states of voltage-gated channels are a closed resting state (C), an open conducting state (O), and a closed inactivated state (I) (Fig. 2.1C). Channels are closed at the resting membrane potential and can be activated by membrane depolarization, which causes an outward move of the voltage sensors relative to the rest of the channel that then opens the “activation gate” over a timescale of milliseconds. With sustained depolarization, a different gate, the so-called “inactivation gate” will close spontaneously. The inactivated channels (i.e. in the ‘closed inactivated state’) will remain refractory to opening and can only recover from this state after a certain period of membrane repolarization (i.e. moved to the ‘resting closed state’). Some

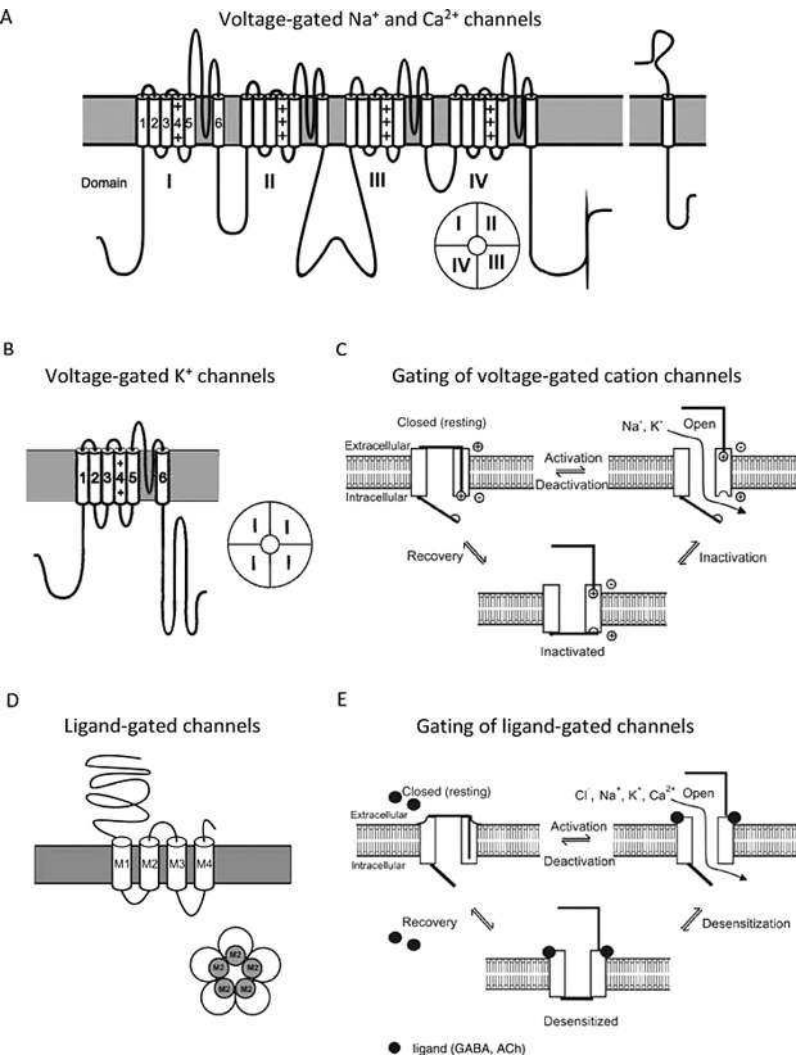


Fig. 2.1 Secondary structure and main conformational states of voltage- and ligand-gated ion channels. (A) The α-subunits of voltage-gated Na⁺ and Ca²⁺ (Na_v and Ca_v) channels consist of four homologous domains (I–IV) each with six transmembrane segments (S1–S6). The S4 segments, located around the ion-selective pore-forming S5–S6 segments, contain positively charged residues conferring voltage dependence to the channel protein. The β-subunits have modulating effects on the function of voltage-gated channels. (B) α-subunits of K⁺ voltage-gated (K_v) channels correspond to a single domain of Na_v and Ca_v channels and assemble into tetramers. (C) Gating of voltage-gated channels. At the resting membrane potential the channels are in the closed state and not permeable to ions. Upon membrane depolarization, the voltage sensors move outward opening thereby the “activation gate” of the channel on a millisecond timescale. After opening of the activation gate, and upon sustained depolarization, some of the channels can close another gate in a process called inactivation. The inactivated channels cannot be directly activated from this state, i.e. they are refractory, and need some time at hyperpolarized potentials before they can be activated again. Membrane repolarization closes the activation gate in a process called deactivation (the illustration is kindly provided by Frank Lehmann-Horn). (D) Ligand-gated ion channels present tetrameric or pentameric structures comprised of subunits having two or four transmembrane segments named M1–M4. The ion-conducting pores are formed by the M2 segments and have a broad ion selectivity being permeable either to cations, as in excitatory nicotinic acetylcholine or glutamate receptors, or to anions, such as in inhibitory GABA or glycine receptors. (E) The three main conformational states of ligand-gated ion channels are open, closed, and desensitized. Ligand-gated channels open from a closed state upon binding of the ligand, for example a neurotransmitter. The ligand binding also enables the desensitization process, which results in channel closure in the presence of the agonist. Removal of the ligand leads to recovery from desensitization. Channel closing of non-desensitized channels is denoted as deactivation.

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types of K^+ channels do not have a closed inactivated state and are constitutively open upon membrane depolarization.

The steep depolarizing phase of an action potential is mediated by activation of the Na^+ inward current, but both fast inactivation of Na^+ channels and activation of K^+ channels, carrying an outward K^+ current, account for the membrane repolarization. Thus, both a disruption of the fast Na^+ channel inactivation (resulting in a gain of function with increased Na^+ inward current) and a decrease in outward K^+ conductance (loss of function) can lead to slowed or incomplete repolarization of the cell membrane and result in spontaneous series of action potentials and neuronal hyperexcitability. The impaired repolarization can indirectly affect the Na^+ channels by keeping them in the inactivated state. This will reduce their availability and can also lead to a so-called “depolarization block,” which will diminish the net activity of the affected neuron. In addition, a loss of Na^+ channel function, for example caused by nonsense mutations predicting truncated proteins or by use-dependent Na^+ channel blockers such as phenytoin, carbamazepine and lamotrigine, and a gain of function of a K^+ channel, as the one caused by the antiepileptic drug retigabine, would be expected to reduce the excitability of the neurons expressing the affected channels.

One of the main roles of neuronal voltage-gated Ca^{2+} channels is the regulation of transmitter release from presynaptic nerve terminals, but they are also important for other processes such as dendritic and somatic signaling, and burst firing in thalamic and other neurons.

Ligand-Gated Channels

Ligand-gated channels are activated by neurotransmitters such as acetylcholine (ACh), glutamate, glycine, or γ -amino butyric acid (GABA), or by nucleotides. These channels are found clustered in the postsynaptic membrane of fast chemical synapses and open rapidly after binding of the agonist. They are constituted by tetrameric or pentameric associations of subunits of similar structure (Fig. 2.1D) comprising two to four transmembrane segments (M1–4). The central pore, formed by the M2 segments, is not as selective as in the voltage-gated channels and conducts either cations in excitatory ACh or glutamate receptors, or anions in inhibitory GABA_A or glycine receptors. The binding of transmitters and the coupling to channel opening are complex processes, which can consequently be influenced by amino acid changes in many different regions of these channels.

Like the voltage-gated channels, ligand-gated channels have three main conformational states: resting, open, and desensitized (Fig. 2.1E). Binding of the transmitter opens the channel from the resting closed state. However, during prolonged presence of the transmitter the channel will be converted to another closed conformational state, the “desensitized” state. Only after removal of the transmitter can the channel recover from desensitization and subsequently become available for another opening. In channels that have not yet reached the desensitized state, removal of the agonist, as caused by chemical modification, for example by acetylcholine esterase or by presynaptic reuptake of the transmitter, induces a faster closing called deactivation. Both processes,

deactivation and desensitization, contribute to the termination of the postsynaptic signal. Their disturbance can prolong excitatory or reduce inhibitory signals, which both result in a hyperexcitability of the postsynaptic membrane and can promote the generation of epileptic seizures.

Subunit Composition, Neuronal Expression, (Sub)Cellular Localization, and Related Functional Aspects of Ion Channels

Pore-forming subunits of both voltage- and ligand-gated ion channels show considerable molecular diversity, which is increased further by the modulating effects of the auxiliary proteins or, as in the case of voltage-gated K^+ or ligand-gated channels, by the ability of the channels to form heteromers bearing distinctive gating characteristics. Their physiological role will therefore depend on their spatial and temporal expression pattern. Although some ion-channel proteins have ubiquitous expression, most of the pore-forming subunits are expressed in a tissue-specific manner. This is the reason, for instance, why mutations in different types of Na^+ or K^+ channel genes can cause myotonia (mutations in the skeletal muscle sodium channel gene *SCN4A*), cardiac arrhythmia with long QT syndrome (mutations in the heart muscle Na^+ channel gene *SCN5A* or the cardiac K^+ channel gene *KCNQ1*), deafness (mutations in the inner ear K^+ channel genes *KCNQ1* and *KCNQ4*), or different forms of epilepsy (mutations in the neuronal Na^+ channel genes *SCN1A*, *SCN2A*, *SCN8A* and *SCN1B*, or the neuronal K^+ channel genes *KCNQ2* and *KCNQ3*) [3,35]. Furthermore, the localization of ion channels in different brain structures, distinctive neuronal or glial populations, or within different intracellular (neuronal) compartments is decisive in determining their physiological effects. Figure 2.2 illustrates the localization of a few selected ion-channel proteins in different types and sub-cellular compartments of neurons. A nice example of the importance of localization and temporal changes during development is provided by the differential expression of Na^+ channels in different types of neurons described in the following paragraph.

Nine different genes encode voltage-gated sodium channel α -subunits, and four of them, *SCN1A*, *SCN2A*, *SCN3A*, and *SCN8A*, encoding $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ proteins, respectively, are highly expressed in neurons of the CNS. Each sodium channel α -subunit associates with one or more β -subunits, $\beta1$ – $\beta4$, which code for transmembrane proteins with a single extracellular loop (Fig. 2.1A) and influence α -subunit trafficking, stability, and channel gating. Na_v1 isoforms are found in different neuronal subtypes and concentrated in axon initial segments (AISs), the site of action potential generation (Fig. 2.2). $Na_v1.3$ are predominantly expressed in embryonic and neonatal but not adult brain in rodents. In the AIS of the optic nerve and principal neurons, $Na_v1.2$ channels are highly expressed early in development and their expression is diminished towards adult ages, whereas $Na_v1.6$ channel expression increases with maturation largely replacing $Na_v1.2$. In adult brain, $Na_v1.2$ is also highly expressed in unmyelinated axons and $Na_v1.6$ is found at nodes of Ranvier [36–38]. In contrast, it