

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

General introduction

PHILIP A. SCHWARTZKROIN

Concepts and models

There is little doubt that advances in epilepsy research are occurring at a rapid rate. For those of us who are interested in understanding the mechanisms underlying epileptiform activities – whether because of a basic interest in how the brain works, or driven by a concern for more effective treatments for the epilepsies – progress in the laboratory has been almost bewildering. It seems that in each new issue of each neuroscience publication there are new insights and possibilities that we must integrate into our old frameworks. Much of the ‘progress’ has been propelled by advances in technology. For example, at the electrophysiological level, new recording techniques such as patch-clamping have allowed investigators to gain much greater detailed understanding of single-cell properties. New antibodies and tract-tracing techniques have provided information about specific cell populations and about plasticity in neuronal interconnections. Molecular neurobiology is beginning to make a considerable impact on epilepsy research, providing techniques for studying the genetics of inherited epilepsies, as well as for examining the structure and expression of channels and receptors. Pharmacological and neurochemical methods now provide highly sensitive means for analyzing receptor populations, and for assaying transmitter systems (e.g., with microdialysis). Clearly, a single volume cannot hope to deal with all this information, not even were we to focus exclusively on ‘new’ data. This explosion of information undoubtedly accounts for the many new books, published within the last few years, with a focus on the epilepsies. Each stakes out its own particular area of interest, and attempts to develop that part of the grand picture. Each volume inevitably reflects the interest and expertise of the participating authors. This volume is no exception.

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

The primary goal of this volume is not simply to review current information. Indeed, the particular areas of interest and technical approaches taken by the authors are secondary. Rather, the authors' major task has been to develop a discussion about key hypotheses that they feel are particularly important in the field of modern epilepsy, to write chapters that focus primarily on concepts and ideas, rather than on results and data. Our hope is that these ideas and concepts will not be outdated in six months, but will continue to be relevant to our studies of the basic mechanisms of the epilepsies.

In some important ways, the development of conceptual frameworks within which to fit experimental data is much more difficult than producing laboratory results. If we survey the current literature on epilepsy, we find an incredible wealth of experimental data – details about how and why cells discharge, how that activity is modulated, what factors influence cell reorganization, etc. It is becoming increasingly clear that virtually anything we learn about normal neuronal activity helps us to understand the basis of epileptogenesis and epileptiform activities. Thus, studies ranging from micro-analysis of channel currents to macro-analysis of lesions to large brain regions have proven to be 'relevant' to epilepsy research. Given such a wealth of data, how does one decide which factors are salient with respect to the various forms of epileptiform activity? We have known for many years that innumerable features of the brain change during development and maintenance of hyperexcitability. How do we tell which features are *causally* related to seizure development, which are *required* for seizure maintenance, and which are simply results of seizure activity? To begin to approach such questions, the investigator must generate conceptual frameworks within which to test specific hypotheses. Then, to translate these ideas to the laboratory, it is necessary to develop 'appropriate' experimental models. The choice of model with which we work, and its connection to the hypotheses developed to explain epileptiform activity, is critical. In fact, the choice of model inevitably influences the conceptual frameworks within which our ideas develop; it is only by developing models that we can test hypotheses.

Twenty years ago, the book *Experimental Models of Epilepsy – A Manual for the Laboratory Worker* (Purpura *et al.*, 1972) was published. Many models were described by investigators who were pioneers in epilepsy research. It is interesting to note that then, as now, the number of available models was impressive. One can only speculate about the drive to develop such a multitude of experimental approaches. One rationale is that there are so many different forms of epilepsy that no one

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)*General introduction*

3

model is sufficient. A rather different view is that these models multiply at random, as though they have a life of their own. Indeed, one of the revelations about possible underlying mechanisms of the epilepsies (and ways to model them) is that epileptiform activity can be produced as a result of many types of experimental intervention. The brain appears to have a rather limited repertoire of behaviors by which to respond to trauma/insult, or to deal with inborn errors. One of the most common responses is for the abnormal region to become hyperexcitable. The activity that we call epilepsy, then, may reflect a basic underlying propensity of the central nervous system.

These two general views of model generation are, I think, less than optimal. The implication of the first line of reasoning is that one develops models to mimic particular clinical phenomena. To do so successfully requires that we can clearly define the salient features of the epileptic brain that should be mimicked in the model. However, it takes only a short time, sitting in a conference of ‘epileptologists’, to discover that there is little agreement about the defining feature of epilepsy. Each investigator has a slightly different, and rather individual, definition – implicit or explicit. We should expect no less, scientific investigation being a human enterprise. The implication of the second approach is that the specific model does not really matter, since similar phenomenology can be reproduced in so many ways.

My own bias is that models are most successful when they are used as a means by which specific problems and questions related to the epilepsies may be approached. Therefore, different models are appropriate for studying different issues. For example, to answer the question ‘Is hyperexcitability always associated with loss of inhibition?’, one would like to examine a number of models in which inhibition was not blocked a priori. A model in which GABAergic inhibition (GABA is γ -aminobutyric acid) was completely blocked, e.g., by bicuculline, would be inappropriate to the question – although not necessarily irrelevant to studies of the epilepsies.

The range of ideas relevant to the generation of epileptiform activity is indeed broad. In this volume, the work reported ranges from the level of receptor molecules and cell membranes to the interaction of long-loop neuronal pathways, and from naturally occurring genetic determinants of epileptiform activity to artificially produced epilepsy models in vitro. Throughout, there is an implicit understanding that abnormal activities can be understood at a variety of levels, each building upon the other as one would build an elaborate castle out of simple building blocks. What constitutes the various blocks contributing to the epilepsy ‘castle’ is the

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

focus of this volume. For the present discussion, I will divide the issue into three major levels of complexity: (a) intrinsic cellular properties, including channel and receptor expression; (b) the interaction of neurons with each other, and with their extracellular environment within a limited region which one defines as the 'focus'; and (c) the involvement of larger populations of neurons, and hence the spread of epileptiform activity from a localized region to broader areas of the brain.

Basic building blocks

Intrinsic cell properties

To think of a neuron as the most basic building block is in some ways misleading, given the apparently endless means by which the activity of a given neuron can be modified. For example, the list of voltage-gated (and ligand-gated) channels that determine cellular properties is continually growing. Each cell type appears to have a unique complement and distribution of these channels, although many of the channels are common across virtually all cell groups. An outline of voltage-gated channels is inevitably incomplete, but gives some hint about how the interaction of even these 'simple' elements can modulate the excitability of a given neuron in a complex manner (Crill & Schwandt, 1983).

The basic Hodgkin–Huxley sodium channel (Hodgkin & Huxley, 1952) is an important component of most neurons, with its rapid voltage-dependent activation and inactivation properties. Recent molecular studies have found, however, that sodium channel subunit construction may divide the channels into at least two subgroups with specific preferential cellular localizations (axon versus soma/dendrite) (Westenbroek *et al.*, 1989). This differential localization of sodium channel subtypes may parallel the distinction between the rapidly inactivating and 'persistent' sodium channels. The latter (Stafstrom *et al.*, 1984), although similar to the Hodgkin–Huxley-type channels in their tetrodotoxin sensitivity, do not inactivate quickly, and are largely activated at membrane potentials just subthreshold for spike discharge. The persistent sodium current can therefore contribute substantially to the efficacy of excitatory postsynaptic potentials in triggering action potentials, or can modulate postsynaptic potential amplitude when those synaptic inputs are subthreshold.

A number of different calcium channels have been described, and an attempt has been made to divide them into three (or four) major types (Nowycky *et al.*, 1985): (a) L-type, with a high activation threshold and

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

slow (if any) inactivation, probably the major contributor to calcium 'spikes' in many cells (Hess, 1990); (b) T-type, with low threshold and rapid inactivation (indeed, normally inactivated at or near resting potential), involved in the generation of rhythmic activities (e.g., in thalamic contribution to absence spike-and-wave activity) (Mogul & Fox, 1991); and (c) N-type, often thought to constitute the major presynaptic terminal population of calcium channels (Tsien *et al.*, 1988). These different calcium channels are distinguishable on the basis of their kinetics, as well as their differential drug antagonist sensitivity: L-type specifically blocked by dihydropyridines (Seagar *et al.*, 1988); T-type blocked by ethosuximide-like drugs (Coulter *et al.*, 1989); and N-type blocked by ω -conotoxin (Plummer *et al.*, 1989). It is clear that the density and distribution of these channels profoundly influence the discharge properties of neurons in the central nervous system (CNS).

The list of potassium-channel-mediated currents is ever-growing; one might well wonder why so many different potassium currents are needed by CNS neurons. Most of the potassium currents are turned on by membrane depolarization, and are hyperpolarizing in function – contributing to spike repolarization, interspike interval, or intervals between bursts of cell activity (Crill & Schwindt, 1983; Storm, 1987). Such currents may be voltage sensitive, e.g., A-currents and delayed rectifier currents (for which there is now molecular evidence of a large variety, although their various functions are by no means clear; Connor & Stevens, 1971; Wei *et al.*, 1990). Another group of potassium currents appears to be modulated by intracellular ion concentrations: calcium dependent (Schwartzkroin & Stafstrom, 1980; producing either long-lasting or brief hyperpolarizing effects) and sodium dependent (Schwindt *et al.*, 1989; which may also contribute long-lasting hyperpolarizations, and apparently reflect cellular discharge during which sodium enters the cell). Finally, there is a voltage-sensitive potassium conductance (I_H) that is generally depolarizing. These anomalous rectifier I_H channels open when the cell is hyperpolarized, and tend to resist further hyperpolarizing drive (Spain *et al.*, 1987).

Interference, blockade, or modulation of any one of these channels could have dramatic effects on the discharge properties of CNS neurons, and thus on the population responses in various parts of the brain. Given that these channels are composed of protein subunits, coded for by specific genetic sequences, alterations/mutations in the genetic machinery could selectively affect one or more of these channels (Wei *et al.*, 1990). More typically, however, neurotransmitter systems (e.g., using cholinergic,

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

noradrenergic, and serotonergic agents) potently and selectively modulate these channels. The growing complexity of these neurotransmitter systems complicates an understanding of these interactions. For example: there are at least two separate receptors for GABA (GABA_A and GABA_B) (Hill & Bowery, 1981; Olsen, 1981; Bormann, 1988; Schofield, 1989); a large number of receptors for excitatory amino acids, including *N*-methyl-D-aspartate (NMDA) and 'non-NMDA' (quisqualate/kainate) ionotropic receptors (Mayer & Westbrook, 1987; Collingridge & Lester, 1989), as well as metabotropic glutamate receptors (Houamed *et al.*, 1991); a variety of noradrenergic (Kobilka, 1992), serotonergic (Peroutka, 1988), and cholinergic (North, 1986) receptors; and 'innumerable' peptide-receptor interactions (Lundberg & Hökfelt, 1983). A detailed listing would be almost impossible, and certainly inappropriate, in this General introduction.

General issues relevant to the interaction between voltage-gated and ligand-gated channels include the following: (a) the function of at least some of the ligand-gated receptors is voltage dependent (Mayer *et al.*, 1984); therefore, voltage-gated channels can influence directly the operation of the neurotransmitter-gated channels; (b) most receptors are coupled, directly or indirectly, to channels which allow ions to enter into and/or exit from the cell. Since some of the voltage-gated channels are ion dependent, neurotransmitters can gate not only the channels to which they are coupled, but also influence other, related, ion-sensitive systems. (c) Many of the transmitter-gated systems engage intracellular second (and even third) messenger systems (e.g., G-proteins) (Andrade *et al.*, 1986), which often involve kinase activation and protein phosphorylation (Chen *et al.*, 1990). It seems quite likely that phosphorylation affects not only the ion channels to which these receptors are coupled, but also receptor molecules (e.g., GABA) or ion channels (e.g., voltage-dependent sodium channels) (Catteral *et al.*, 1990) that are not coupled to receptors. We know relatively little about how the various phosphorylation steps modulate cell excitability; however, phosphorylation of specific membrane-associated proteins does appear to be critical in the development of normal synaptic plasticity – at least as modeled by long-term potentiation.

Since the complexity of these voltage-, ion-, and transmitter-sensitive channels in the membrane of each neuron has become so difficult to comprehend at an intuitive level, their function is now often approached within the context of computer models of single neurons. When considered as units of epileptiform activity – i.e., as basic building blocks of a more

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)*General introduction*

7

elaborate system – this single-cell complexity is quite impressive. It is therefore not surprising that some investigators have described ‘epileptic’ neurons’, and posed hypotheses regarding single-cell ‘seizure’ generation (Segal, 1991). This focus on single neurons is reminiscent of analyses traditionally carried out by neurobiologists interested in pacemaker activity in invertebrates (Connor, 1982). Clearly one can elicit bursting activity in single isolated neurons via a variety of manipulations. Even within this simplified single-cell context, however, it is difficult to determine which cell features are salient in the generation of epileptiform activity. The critical question remains: can a single neuron really be epileptic?

Local interactions

Further insight into issues of epileptogenicity necessarily involves the study of populations of neurons. This second step in building the epilepsy ‘castle’ deals with how the blocks fit together. Within a local environment, how do the cells interact? What is the nature of the connectivity and how is it modified and/or influenced by the extracellular environment? Much of the current investigation into mechanisms of epileptogenesis falls within this category. For example, an investigator may ask, ‘How do neurotransmitter substances affect the excitability of a given neuronal population?’ This question is certainly related to the issue of how a drug might affect an individual neuronal building block. However, as we consider the role of transmitters/modulators in ‘circuitry’, the issue is not only how a given transmitter gates channels *within* single-cell membranes, but also how it changes the likelihood of *output* from a given neuron – and thus increases or decreases cellular interaction within the population. A given transmitter may give rise to a number of different such effects. For example, GABA can produce inhibition or ‘excitation’, depending on where and how much of the drug is released, the maturity of the system in which it is tested, and the types of receptor upon which it acts (Alger & Nicoll, 1982; Mueller *et al.*, 1982; Michelson & Wong, 1991). Effects of other transmitters, acting on diverse sets of receptors, can be even more complex. For example, the net effect of norepinephrine on individual cortical building blocks often appears to be excitation, mediated through beta-receptors (Madison & Nicoll, 1986). Beta-receptor activation leads to a loss of cell afterhyperpolarizations and a decrease in cell accommodative properties – which increases the cell’s responsiveness to incoming excitatory stimuli. However, when analyzed within the context of the

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

intact CNS, noradrenergic action is more often inhibitory than excitatory. For example, lesions of the noradrenergic system generally produce animals that are significantly more prone to seizure than is the norm (McIntyre & Edson, 1981).

Perhaps the most excitement in this area of neurotransmitter effects on cell excitability has come from recent investigations of the NMDA receptor. Studies suggest that, at least in some models such as kindling, NMDA receptor function is significantly enhanced (Mody *et al.*, 1988). Since NMDA receptor function is modulated by a number of different binding sites on the NMDA receptor/ionophore molecule (Williams *et al.*, 1990), modulation of this important receptor may occur through a variety of cellular pathways. The relationship between NMDA and non-NMDA receptors, their respective roles in various hyperexcitability phenomena, and the possibility that non-NMDA receptors are potentiated via NMDA-mediated mechanisms during stimulation (Muller & Lynch, 1988) (or as a result of discharging seizure foci) are issues of critical importance that involve an understanding of cellular interactions.

Other recent studies of cell–cell interactions focus on circuitry requirements for producing synchronized discharge activity (one of the characteristics of epileptiform discharge). Modeling work started in the early 1980s (Traub & Wong, 1981) suggested that even a small degree of recurrent excitatory interconnection within a local cell group (for example, in the CA3 region of hippocampus) was sufficient to mediate synchronized discharge. Occurrence of such discharge was based, in part, on the intrinsic properties of the participating neurons, and mediated by the excitatory interactions among the cells. Although it is unclear how common the functional recurrent excitatory interactions normally are within cortical areas of the CNS, both hippocampal and neocortical regions show significant excitatory interactions when inhibition is reduced (Christian & Dudek, 1988). Further, even in the absence of normal excitatory interconnections, it is possible that emergent recurrent excitatory collaterals – i.e., sprouting fibers – may be important contributors to the development of synchronized hyperexcitability (Cronin & Dudek, 1988). Synchronized excitatory drive may result either from potentiation of already-existing synaptic contacts, or the development of new contacts through ‘plastic’ mechanisms.

Perhaps the oldest of the hypotheses developed to ‘explain’ epilepsy focuses on inhibitory control (mediated via GABA receptors) within neuronal populations, with the loss of inhibition seen as the critical step in development of hyperexcitability (Schwartzkroin & Prince, 1980;

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)*General introduction*

9

Schwartzkroin & Wyler, 1980). The inhibition story has, however, become exceedingly complex. The nature of the inhibition within any given brain region depends on the existence of inhibitory (often GABAergic) interneurons (Lacaille *et al.*, 1989) that make divergent connections to the principal cells in each region, and that receive convergent inputs from principal cells. The function of these interneurons – i.e., their modulation of principal cell output – depends on their patterns of connectivity with other cells in the local region. Inhibitory interneuron connections with other inhibitory interneurons, as well as with excitatory cells, endow the system with innumerable points of control. The recent interest in the role of GABA receptors on presynaptic terminals now adds even more complexity to the system (Thompson & Gähwiler, 1989).

We can delineate many ways of producing inhibition or excitation by manipulating the interneuronal inhibitory circuit. For example, if inhibition were produced only by postsynaptic contacts of interneurons onto pyramidal cells, then loss of those interneurons – or diminished effectiveness of the pathway by which the interneurons are excited – would yield net excitation in the system. If, on the other hand, interneurons also made strong connections with other inhibitory interneurons, then loss of drive onto the initial interneuron population might yield greater net inhibition onto pyramidal cells, as a result of the ‘release’ of the second inhibitory population. If we then add the effects of presynaptic GABA receptors on either excitatory or inhibitory terminals (or both), the various scenarios multiply exponentially. Finally, and realistically, the investigator must face the likelihood that changes in inhibitory (or excitatory) circuitry are not all-or-none, and thus must be evaluated quantitatively. How much inhibition must be lost to produce hyperexcitability (Chagnac-Amitai & Connors, 1989)? How much excitatory interaction is necessary to synchronize a cell population?

CNS plasticity is another important factor that influences how interaction among neurons may give rise to epileptiform phenomena. One question that highlights the critical nature of this plasticity is ‘What happens to tissue excitability when a part of the nervous system is damaged (Meldrum & Corsellis, 1984), as seems often to be the case in epileptic brain?’ In building a castle of wooden blocks, if we remove a number of critically located individual blocks, the entire castle is likely to collapse. Such a collapse does not occur often in the CNS, perhaps because there is so much ‘redundancy’. It is clear, however, that the CNS also displays a strong capacity for replacing lost elements with

Cambridge University Press

978-0-521-03350-3 - Epilepsy: Models, Mechanisms, and Concepts

Edited by Philip A. Schwartzkroin

Excerpt

[More information](#)

newly grown processes (sprouting). Can new processes replace lost elements in a functionally adaptive manner, or is the plasticity likely to be dysfunctional? How do these changes bias the general excitability of the region?

Cell-cell interaction is significantly impacted by contributions from the extracellular environment. Experimenters have long known that tissue excitability is dramatically affected by changes in extracellular ionic concentrations. Increases in potassium concentration (which may result from prolonged cell discharge) may produce further hyperexcitability (Rutecki *et al.*, 1985). Lowering of the extracellular calcium concentration leads to a loss of synaptic drive (since transmitter release is dependent on calcium influx), but may also (at least in some tissues) result in spontaneous synchronized cell discharge (presumably via non-synaptic mechanisms) (Konnerth *et al.*, 1986). Both this calcium effect and the effects of extracellular potassium are probably modulated by changes in the extracellular space (Traynellis & Dingledine, 1989). Decreased extracellular space, as might occur when cells swell (e.g., as a result of prolonged discharge and the subsequent entry of sodium and water into neurons), significantly magnifies changes in extracellular ion concentrations. Potassium release into a decreased extracellular space is even more likely to increase excitability, thus contributing to a 'positive feedback' cycle. A small extracellular space, in addition, magnifies the effects of extracellular current flow. The effects of this current, the basis of so-called ephaptic interactions among cells (Taylor & Dudek, 1984), is to help to synchronize discharge in cell populations, and to excite cells that are only marginally depolarized by direct synaptic interactions. In addition to these extracellular factors, one must consider glial contributions. Glia have traditionally been thought to be important in the uptake of extracellular potassium (Dietzel *et al.*, 1989). The infiltration of glia into damaged tissue may impact directly on the excitability of the region – from the mechanical effects of interposed glial elements between neuronal processes, or by altering the normal potassium distribution. The function of glia, based on their active ionic conductances, has also been hypothesized; for example, calcium conductances have been demonstrated in glia (MacVicar, 1984), and waves of calcium flux investigated with optical imaging techniques. Given the importance of calcium function in controlling normal neuronal excitability, the occurrence of such calcium activity in glia suggests an important coupling between neurons and glia in normal CNS function. Loss of appropriate glial controls may give rise to regions of abnormal neuronal activity.