Acquired Ion Channel Dysfunction in Epilepsy

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Introduction

That ion channel dysfunction lies at the root of epilepsy has for decades seemed a self-evident truth. Ion channels, both voltage- and ligand-gated, mediate the excitable behavior of neurons, and since seizures result from neuronal hyperexcitability, surely altered biophysical properties or expression of ion channels must underlie this pathological hyperexcitability. Actual proof of this dogma, however, did not arrive until 1995, with the first publication of a genetic locus found in a human epilepsy syndrome, a mutation in nicotinic acetylcholine receptors underlying autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Since 1995, a number of other idiopathic human epilepsy syndromes have been conclusively linked to single gene mutations (**Table 1**). Of note is the fact that all of these genes code for ion channel subunits or presumptive accessory subunits. The alterations of ion channel properties caused by these mutations are diverse, and include loss of expression or function (haploinsufficiency) as well as alterations that influence function of channels assembled from heteromeric subunits (a dominant negative action). The importance of these findings cannot be overstated: they prove that defects in individual ion channel subtypes can produce human epilepsy syndromes, complete with characteristic developmental courses and responses to antiepileptic drugs.

Does ion channel dysfunction similarly underlie epilepsy arising from acquired causes, such as head injury, brain tumors, or cerebral hemorrhage as it does in genetic epilepsy? (Temporal lobe epilepsy (TLE), the most common cause of epilepsy in adults, is widely assumed to also be an 'acquired epilepsy.') It is reasonable to hypothesize that ion channel dysfunction forms the final common pathway resulting from a variety of acute insults to the CNS. However, unlike the case for some genetic human epilepsy syndromes, proof of this concept is still lacking. Reasons for our slow progress in testing this hypothesis include the relative inaccessibility of human brain tissue from patients with epilepsy – unless they come to epilepsy surgery – with which to study ion channel function (compared with the relative ease of finding pathology in a patient's genomic code). Also problematic is the lack of control data from unaffected patients. Thus, animal modeling is the principal means of studying the causes of acquired epilepsy.

Background

The animal models in wide use present a range of advantages and disadvantages in their similarity to human epilepsies. Models that replicate typical CNS insults would seem the best candidates to study the biological processes underlying the induction of the epileptic state, or epileptogenesis. However, experiments thus far with rodent models of traumatic brain injury, cerebral hemorrhage, hypoxic–ischemic encephalopathy, and febrile seizures have produced animals with relatively mild epileptic phenotypes – with either subtle partial or subclinical seizures, an epilepsy course that may remit over time, or even no evidence of spontaneously recurring seizures. Thus, the most widely used models are the poststatus epilepticus (SE) models involving induction of SE by pilocarpine or kainate. These models produce a robust epileptic phenotype in rodents, with spontaneously recurring seizures that span (or exceed) the Racine scale (a behavioral measure of seizure type/severity), and which do not remit over time. Like human acquired epilepsy, there is a variable 'latent period' between the insult and the development of spontaneous seizures, although the duration of this period is dependent on model methodology and in some cases may be just a few days; also like human TLE, these post-SE models produce hippocampal pathology reminiscent of medial temporal sclerosis. A significant drawback to these models is their lack of a naturalistic insult: humans are rarely exposed to chemical convulsants, and it is unclear how status epilepticus is related to traumatic brain insult (or to TLE). It has been argued that post-SE models are relevant because some human cases of adult TLE are associated with a history of febrile SE as a child, but this finding is the exception rather than the rule.

An additional rationale for the use of post-SE models of epilepsy pertains to the doctrine of 'seizures beget seizures.' This idea, that the natural course of untreated epilepsy shows an accelerating seizure frequency, dates to observations of Gowers in the nineteenth century and suggests that successive seizures alter brain excitability in such a way as to make further seizures more likely. If true, one mechanism by which this progression might occur is through seizure-dependent modification of ion channel properties that results in increased neuronal excitability. Although 'seizures beget seizures' is an

t0005 **Table 1** Human genetic epilepsy syndromes resulting from ion channelopathy

Syndrome	*Affected genes*
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	*CHRNA4*, *CHRNB2*
Benign familial neonatal convulsions (BFNC)	*KCNQ2*, *KCNQ3*
Generalized epilepsy with febrile seizures plus (GEFS+)	*SCN1B*, *SCN1A*, *GABARG2*
Severe myoclonic epilepsy of infancy (SMEI)	*SCN1A*
Benign familial neonatal–infantile convulsions (BFNIC)	*SCN1A*
Idiopathic generalized epilepsy and episodic ataxia	*CACNB4*
Autosomal dominant partial epilepsy with auditory features (ADPEAF)	*LGI1*

oft-quoted dictum, there is little clinical proof supporting it. While retrospective clinical observations do show that the interval between seizures tends to decrease for the first several seizures after the onset of epilepsy (but before treatment), a definitive prospective test of this hypothesis is impossible for ethical reasons. In animal models of acquired epilepsy, such as kindling, kainate, and fluid percussion injury, there is clear evidence that seizure frequency and intensity increase after the initial insult, eventually achieving a plateau level. Whether the accelerating seizure rate seen is seizure-dependent, or instead reflects an underlying progressive process of epileptogenesis set in motion by the initial insult, is unclear. This question can be experimentally tested by pharmacologically blocking seizures during the early period after the insult, when an accelerating seizure frequency would be expected. Then, after the antiepileptic treatment is discontinued, it can be determined whether seizures begin at their usual low, accelerating rate, or whether they immediately begin at their higher plateau frequency. An interesting example of this test comes from a study in the WAG/Rij rat model of generalized epilepsy in which blockade of seizures during the period when they make their spontaneous developmental appearance significantly decreases their age-dependent frequency after the antiepileptic drug is discontinued. This finding suggests that for one model of epilepsy with a genetic basis, spontaneous seizures appear with an accelerating time course that is independent of underlying developmental processes. Conclusive data for acquired epilepsy models on this question are thus far lacking.

p0025 Thus, there are multiple ways in which acquired alteration of ion channel function can contribute to epileptogenesis – either as a fundamental cause of hyperexcitability or as a mediator of the process in which spontaneous seizures progressively worsen the course of epilepsy. It is also possible that some ion channel alterations retard the development of epilepsy. When interpreting studies of ion channel property changes in epilepsy models, it is important to consider whether the changes seen reflect a seizure-dependent process occurring after the onset of epilepsy, or whether they are instead set into motion by the initial insult and precede the onset of seizures. A further question is whether the changes seen are likely proconvulsive versus homeostatic. That is, do these changes demonstrably increase the excitability of neurons, or do they diminish intrinsic excitability in an attempt at maintaining brain normality? With these thoughts in mind, we can consider recent evidence for acquired ion channel changes in various animal models of epilepsy.

Methods

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p0030 The results described later derive from a survey of the literature published in the last 12 years using animal models of acquired epilepsy to study altered ion channel properties with electrophysiological, biochemical, and molecular biological techniques.

Results – Specific Ion Channel Changes in Epilepsy

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Na^+ Channels

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p0035 Na^+ channels represent an obvious target of seizure-induced plasticity. Gain of function mutations in the α subunit of Nav1.1 channels or the accessory β1 subunit have been implicated in the inherited human epilepsy syndrome GEFS+; these mutations generally cause an increase in I_{Na}, the current mediated by Na^+ channels, either through slowed or incomplete voltage-dependent inactivation. In contrast, a significant loss of I_{Na} is seen in the progressive human epilepsy syndrome SMEI. This counterintuitive result may be explained by a selective loss of Na^+ channels in cortical interneurons, rather than in principal neurons, leading to diminished inhibition.

p0040 Acquired changes in I_{Na} in dentate granule cells (DGCs) have been seen after pilocarpine-induced SE, with voltage-clamp recordings showing a hyperpolarizing shift in I_{Na} activation coupled with a depolarizing shift in fast inactivation, producing a net increase in the 'window current,' or current activated at physiological potentials. Measurement of mRNA from microdissected dentate gyrus extracts, at dates postpilocarpine that were comparable to the physiological experiments, shows downregulation of Nav1.2 and 1.6 transcripts, along with the β1 accessory subunit. There does not appear to be any change in DGC I_{Na} current density corresponding to the decreased transcription of Nav subunits, but the loss of β1 transcription is possibly consistent with the depolarizing shift in I_{Na} inactivation.

p0045 An intriguing related question is whether ion channel plasticity in epilepsy affects the response to antiepileptic

drugs (AEDs), most of which have been hypothesized to act through direct modulation of ion channels, especially Na^+ channels. Examination of tissue from both epileptic rats and humans undergoing temporal lobectomy has found that epilepsy diminished the inhibitory actions of carbamazepine (CBZ) on I_{Na}. Specifically, the reduction in rate of recovery from inactivation that CBZ induces under normal conditions is nearly absent in DGCs from epileptic tissue. The effect of CBZ in shifting I_{Na} voltage dependence in a hyperpolarizing direction, however, is maintained under epileptic conditions. These results suggest that changes to Na^+ channels in epilepsy render them less susceptible to AED actions, possibly contributing to medical intractability. However, it is unclear which of the actions of CBZ on I_{Na} are most important in reducing neuronal excitability. Another issue that limits interpretation of some in vitro studies is the relatively high concentrations of drug used to study biophysical actions, often an order of magnitude higher than clinically relevant concentrations seen in human cerebrospinal fluid. Nonetheless, studies of AED action in epileptic animals raise the important question of whether 'epileptic ion channels' might themselves be a different pharmacologic target than the native or heterologously expressed channels usually studied under normal conditions.

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Ca^{2+} Channels

p0050 Upregulation of Ca^{2+} channel activity has been shown in experimental acquired epilepsy in a number of studies. This work began with the observation that during the chronic phase of epilepsy induced by pilocarpine, the proportion of 'bursting' (i.e., firing of multiple action potentials from a single short depolarizing current injection) CA1 hippocampal pyramidal neurons increased from <5% to nearly 50% of cells. Low-threshold T-type currents have been implicated on physiological and pharmacological grounds, with an increase in T-current density. When activated, this augmented T-current could mediate a depolarizing potential that promotes burst AP firing. In accord with prior work that had shown localization of low-threshold Ca^{2+} currents to the apical dendrites of pyramidal neurons, focal application of the T-channel blocker Ni^{2+} to the dendrites abolishes bursting, while application to the soma does not. It is interesting that this condition represents an acquired channelopathy confined to the apical dendrites, one of several examples to be discussed later. There has been no evidence thus far as to the mechanism underlying the upregulation of T current. Because the AED ethosuximide blocks T-channel activity, this work would suggest that ethosuximide, already used against absence epilepsy, might also be effective in temporal lobe epilepsy; however, there is no clinical evidence presently supporting this idea.

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K^+ Channels

p0055 Bertil Hille commented in his classic textbook that K^+ channels were like the 'stops on an organ,' able to fine-tune neuronal excitability by their diverse biophysical properties. Somewhat surprisingly then, K^+ channel dysfunction has been underrepresented in genetic epilepsy, with only one syndrome (BFNC) clearly due to K^+ channel mutation. In experimental acquired epilepsy models, however, a number of changes in K^+ channel activity have been identified, some of which appear to be proconvulsive, while others appear to represent a homeostatic change.

p0060 An important milestone in the study of ion channel properties was the recognition that many ion channel species in pyramidal neurons are distributed in highly nonuniform somatodendritic patterns. The A-type (or transient) K^+ current was the first example, found to exist in pyramidal neuron dendrites in a density gradient pattern, with the apical dendrites containing a sevenfold higher density than the soma. The high dendritic density of rapidly activating Kv4.2 channels (the main channel type underlying the A-current in pyramidal neurons) reduces the amplitude of excitatory postsynaptic potentials, activity-evoked intracellular Ca^{2+} transients, and backpropagating dendritic action potentials. The dendritic location of Kv4.2 channels, while directly influencing integration of dendritic synaptic potentials, also hampers electrophysiological study. However, measurements of Kv4.2 channel expression in chronic epilepsy (i.e., tissue from postpilocarpine rats) have shown that Kv4.2 channel number is diminished by about one-third, as quantified by both Western blotting and mRNA expression. The electrophysiological consequence of the loss of A-current is increased AP backpropagation in the dendrites, potentially allowing increased opening of other voltage-gated channels such as Ca^{2+} channels. An interesting additional finding is that the Kv4.2 channels that remain in this tissue are more phosphorylated at a site that is recognized by the extracellular stimulus-related kinase (ERK). Phosphorylation by ERK of Kv4.2 shifts the voltage-dependent activation of these channels to more depolarized levels, diminishing their activity. Thus, the Kv4.2 channel dysfunction seen in this model of chronic epilepsy is twofold: a loss of channel number, and downregulation of the channels that remained.

p0065 Whether or not changes in Kv4.2 function are a significant contributor to the epileptic phenotype remains to be seen. Despite its significant role in dendritic physiology, a knockout of Kv4.2 by itself does not appear to cause obvious seizures in the transgenic animals. One possible explanation for this observation is that there is upregulation of other Kv channels (i.e., non-Kv4.2) that can mediate transient A-type currents in Kv4.2 knockout mice; these currents, putatively mediated by the Kv1 family and localized to the cell soma or axon initial segment, may

counteract the loss of dendritic Kv4.2 channels. Also, because Kv4.2 expression has been measured only in the chronic phase of epilepsy, it is unclear whether the loss of A-currents is a cause or a consequence of ongoing seizures. Indeed, one study has found that Kv4.2 mRNA expression was reduced by pentylenetetrazole-induced seizures alone, in the absence of established epilepsy.

p0070 Another K^+ channel modulated by seizures is the Kv2.1 channel that produces a delayed rectifier current. Unlike Kv4.2, Kv2.1 is localized to the soma and proximal apical and basal dendrites, and it appears to depress excitability during periods of repetitive action potential firing. Shortly following kainate-induced SE, several changes in the localization and biophysical properties of Kv2.1 channels occur. For example, their distribution on the somatic membrane transforms from clusters of ion channels to a more diffuse pattern, without a loss of overall density. Further, the voltage-dependent activation of I_K (the delayed rectifier current mediated in part by Kv2.1) shifts in a hyperpolarizing direction, potentially increasing I_K activation. These changes in Kv2.1 properties are mediated by glutamatergic stimulation followed by calcineurin-dependent dephosphorylation of a number of residues on Kv2.1 itself. These changes reflect a putative signaling pathway by which seizure activity can produce acute changes in ion channel properties. Unlike the changes seen in Kv4.2 with epilepsy, it would be predicted that upregulation of Kv2.1 activation would act in a homeostatic, anticonvulsant fashion. (It is not clear what the effect of declustered Kv2.1 channels would be on excitability.) Also, the changes in Kv2.1 were induced by SE, but were not assessed in animals after the development of epilepsy; thus, it was not determined if they persisted beyond the acute SE-related phase in the kainate model. Indeed, the declustering of channels is observed to gradually revert to near-control levels several hours following stimulation. However, these studies provided solid mechanistic evidence for the links between seizures and ion channel modifications, and lay the groundwork for investigation of these mechanisms in chronic epilepsy.

s0040 HCN Channels

p0075 Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels seem unlikely candidates for a pathogenic role in epilepsy. Originally, identified in the sinoatrial node as a key regulator of heart rate, they have since been found widely in brain, with the HCN1 subtype distributed primarily to neocortex and hippocampus, while the HCN2 subtype is found in subcortical regions such as thalamus. Recent evidence has implicated dysfunction of these channels in both genetic and acquired epilepsy. Genetic loss of function of HCN channels clearly causes epilepsy; knockout of the HCN2 channel produces a generalized epilepsy phenotype in rodents, while inbred rat strains with epilepsy demonstrate altered function of both HCN2 and HCN1 channels. It is unclear whether knockout of the HCN1 channel also produces an epileptic phenotype, although anecdotal evidence suggests that HCN1 knockout mice lack spontaneous seizures but show more severe seizures provoked by kindling or pilocarpine. To date, no human genetic epilepsy pedigrees have been associated with HCN channel mutation.

p0080 There is increasing evidence that acquired experimental epilepsy is associated with altered HCN channel function and expression. One of the first studies to make this association found an increase in I_h, the current mediated by HCN channels, in hippocampal pyramidal neuron somatic recordings after hyperthermia-provoked seizures. However, like Kv4.2 and T channels, HCN channels are predominantly localized to the apical dendrites of pyramidal neurons, so it was of particular interest that subsequent studies, measuring dendritic I_h, found that HCN channels show an acute loss of expression within the first week post-SE. This loss of expression is maintained in chronic epilepsy, and is associated with a hyperpolarizing shift in voltage-dependent gating that further downregulates I_h. (Since HCN channels are activated with hyperpolarization, a hyperpolarizing shift in activation reduces the amount of I_h present at resting potential.) Interestingly, when recurrent seizures post-SE are blocked with phenobarbital administration, the altered HCN channel gating reverts to normal, while the loss of HCN channel expression persists. This result suggests that there are separate mechanisms of HCN channel downregulation in epilepsy, some clearly dependent on ongoing seizures, and not integral to epileptogenesis per se. Similar caveats may apply to other observed changes in ion channel function.

p0085 Changes in HCN channel function in epilepsy, at least for pyramidal neurons, represent another example of ion channelopathy confined to the dendrites, similar to that seen for A-type K^+ channels. The mechanisms underlying the loss of dendritic HCN and A-channel expression are unclear; although there is evidence that HCN1 channel transcription is chronically reduced following hyperthermia-provoked seizures, the rapid loss of dendritic HCN channels (with 24-h post-SE) suggests additional, probably posttranslational mechanisms. In pyramidal neurons, HCN channel downregulation produces neuronal hyperexcitability, although this is not as straightforward to demonstrate as it is for Na^+ and K^+ channels – given the sometimes conflicting influences of I_h on neuronal input resistance, time constant, and resting membrane potential.

$GABA_A$ Receptors s0045

p0090 Blocking inhibition mediated by $GABA_A$ receptors ($GABA_A$Rs) reliably provokes seizures in in vitro and in

vivo models of epilepsy. Thus, it would be expected that alterations of $GABA_A$Rs are well represented in genetic and acquired epilepsy. In fact, there are several reports of human pedigrees of generalized epilepsy associated with loss of function of various $GABA_A$R subunits. Good evidence also exists for acquired alteration of $GABA_A$Rs in experimental models. Because $GABA_A$Rs are composed of five subunits in varying combinations, numerous possibilities exist for altered $GABA_A$R function through differential up- or downregulation of its component subunits. A careful study of this phenomenon in the pilocarpine model has found that α1 and β1 subunit expression in dentate granule cells is decreased in the latent period prior to the onset of seizures, with increases in δ and ε subunits. These changes are maintained in the chronic phase of epilepsy and appear to contribute to increased Zn^{2+} sensitivity of $GABA_A$Rs. Because Zn^{2+} diminishes $GABA_A$R function, this change promotes hyperexcitability.

p0095 Contrasting findings with regard to the δ $GABA_A$R subunit have been seen using the pilocarpine model in mice. Immunohistochemistry in DGCs has found a diffuse loss of δ subunit labeling, beginning in the latent period postpilocarpine, and continuing into the chronic phase. Interestingly, δ subunit expression is increased in dentate gyrus interneurons. It is unclear how to explain the contrasting findings of these two studies; differing methods to measure $GABA_A$R subunit expression may contribute to these differences. However, the recent correlation of δ subunit-containing $GABA_A$Rs and extrasynaptic, tonic inhibitory currents suggests that these channels may mediate a component of GABAergic inhibition that is not subject to the phasic rundown shown by non-δ-containing receptors. Thus, the loss of δ subunits may constitute an additional mechanism by which selective changes in subunit expression could influence neuronal excitability through attenuation of a steady-state inhibitory current.

p0100 Downregulation of GABAergic function has also been seen in a model of perinatal hypoxia. While this model in itself does not produce epilepsy, it does produce persistent neuronal hyperexcitability, and this study is instructive for the mechanisms found to underlie altered inhibition. Acutely following a hypoxic episode in immature rats, evoked IPSCs in CA1 hippocampal pyramidal neurons are decreased. This effect is dependent both on Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors, and activation of the serine-threonine phosphatase calcineurin. Correspondingly, calcineurin activity is increased postseizure and the phosphorylation of $GABA_A$R β2 and β3 subunits is also decreased (although it is not clear that these subunits are responsible for the decrease in IPSCs observed). This work points to signaling pathways, such as calcineurin, that might be acutely activated following status epilepticus. Identification of such mechanisms underlying the induction of ion channelopathy after a neural insult is a significant advance, for it opens the possibility of future therapeutic advances that might target these pathways. For example, phosphorylation signaling is an active area of clinical drug development, with numerous inhibitors of kinases and phosphatases either in preclinical testing, or in a few cases, already in clinical use (e.g., FK-506, an inhibitor of calcineurin used for immunosuppression in organ transplant). These agents are useful tools to test whether interruption of the signaling that underlies acquired channelopathy might prevent the ion channel alterations, and perhaps influence epileptogenesis as well.

Future Directions s0050

p0105 The studies described here clearly demonstrate that experimental acquired epilepsy is associated with alterations in both voltage-gated and ligand-gated ion channel expression, including their biophysical properties. It is tempting to conclude that, as with genetic epilepsies, these changes in ion channel properties underlie the basis of neuronal hyperexcitability that produces seizures. But the situation with acquired epilepsy is not nearly so straightforward as with genetic epilepsy, and there are numerous challenges to be surmounted before we understand how *acquired* channelopathy contributes to epilepsy. While the genetic epilepsy literature shows that alteration of the properties of a single species of ion channel is sufficient to cause a human epilepsy syndrome, the sheer number of ion channel changes observed in acquired epilepsy makes it unlikely that any one of them is causative on its own. The post-SE models used in experimental epilepsy induce a diffuse insult to the CNS that triggers widespread changes in neuronal function and viability. Associated with these changes in cell properties are multiple changes in ion channel function – some of which may contribute to epileptogenesis, some which may cause hyperexcitability but which may not influence epileptogenesis, and some of which may be homeostatic in nature, opposing the induced hyperexcitability.

p0110 To better understand how acquired channelopathy contributes to the induction and maintenance of the epileptic state, we will need to study ion channel changes at a more comprehensive level of detail than has often applied. One issue is that the course of epileptogenesis in the different experimental models is still to be detailed and 'validated'; thus, an assumption that a given ion channel change is occurring during the latent phase (and may be contributing to epileptogenesis) may be unwarranted. Measuring the onset of spontaneous seizures, using chronic video-EEG

recordings, is a time-consuming but important step to determine the true extent of the latent period and to identify ion channel changes that are relevant.

p0115 Another question is whether ion channel changes observed in chronic epilepsy are independent of ongoing seizures. This point can be tested with periods of AED treatment after epilepsy is established. A change in ion channel properties that occurs before the onset of seizures and persists after seizure suppression is a possible contributor to epileptogenesis, while those that revert to normal after AED treatment are likely to be a result of the epileptic activity – although they may be involved in the maintenance of the epileptic state by promoting hyperexcitability. Another issue that often remains unproven in experimental epilepsy is whether alteration of a given ion channel actually causes hyperexcitability. While it might be assumed that a downregulation of K^+ channel activity or an upregulation of Na^+ activity is necessarily proconvulsive, counterintuitive examples abound – for example, the loss of I_{Na} in most cases of SMEI, and a recent description of a gain of function in a Ca^{2+}-activated K^+ channel in a genetic epilepsy pedigree.

p0120 Finally, evidence for a causative role of ion channelopathy in epileptogenesis will be strengthened by demonstration that reversing the channelopathy modifies the course of epileptogenesis. A recent exciting example of this approach was illustrated using gene therapy to increase expression of downregulated $GABA_AR$ subunits, delaying the onset of spontaneous seizures post-SE. Continuing advances in understanding the molecular mechanisms underlying acquired channelopathy offer the promise that similar benefits might result from pharmacological blockade of signaling intermediaries, such as calcineurin. Such clinical applicability, of course, remains the ultimate goal of understanding the process of epileptogenesis – the hope of intervening to prevent epilepsy after an acute insult to the CNS.

See also: Intrinsic properties of neocortical neurons relevant to seizure discharges (00004); Posttraumatic models (00148); Development of surrogate markers for epileptogenesis (00149); Proteomic approaches to the analysis of protein alterations at the synapse in kindling (00231); Post-translational modifications of ion channels in epilepsy (00337).

Further Reading

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