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Curing epilepsy: Progress and future directions

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Abstract

During the past decade, substantial progress has been made in delineating clinical features of the epilepsies and the basic mechanisms responsible for these disorders. Eleven human epilepsy genes have been identified and many more are now known from animal models. Candidate targets for cures are now based upon newly identified cellular and molecular mechanisms that underlie epileptogenesis. However, epilepsy is increasingly recognized as a group of heterogeneous syndromes characterized by other conditions that co-exist with seizures. Cognitive, emotional and behavioral co-morbidities are common and offer fruitful areas for study. These advances in understanding mechanisms are being matched by the rapid development of new diagnostic methods and therapeutic approaches. This article reviews these areas of progress and suggests specific goals that once accomplished promise to lead to cures for epilepsy.

Keywords

Genetics; Epileptogenesis; Co-morbidities; Therapeutics

1. Introduction

During the past decade, substantial progress has been made in delineating clinical features of the epilepsies and the basic mechanisms responsible for these disorders. Eleven human epilepsy genes have been identified and many more are now known from animal models. Candidate targets for cures are now based upon newly identified cellular and molecular mechanisms that underlie epileptogenesis – the process in which the normal brain is transformed into one that generates seemingly unprovoked seizures. Many of these advances have been driven by the development of clinically relevant experimental models. However, epilepsy is increasingly recognized as a group of heterogeneous syndromes characterized by other conditions that co-exist with seizures. Cognitive, emotional and behavioral co-morbidities are common and offer

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fruitful areas for study. These advances in understanding mechanisms are being matched by the rapid development of new diagnostic methods and therapeutic approaches, and the invention of devices that can selectively target not only brain regions but even abnormal cells in the epileptic nervous system.

This article reviews these areas of progress and suggests specific goals that once accomplished promise to lead to cures for epilepsy. The accomplishments reviewed here reflect a highly focused set of goals developed by the international medical/scientific community to find cures for epilepsy (see Acknowledgments), where a cure was defined as (1) prevention of epilepsy in people at risk and (2) effective and safe treatment ("no seizures, no side effects") for individuals with epilepsy [1].

2. Genetics

Genetic strategies applied over the last decade have dramatically reshaped the clinician's diagnostic approach to seizure disorders and opened the biology of inherited forms of epilepsy to molecular and cellular analysis. Epilepsies arise at various ages from both rare monogenic, and more common complex inheritance. At least 11 genes have now been identified for monogenic forms of idiopathic epilepsy (i.e., syndromes in which there is no identifiable causative lesion), and over 50 more genes related to idiopathic epilepsies have been identified in mouse models. Almost all of these genes encode ion channels or proteins associated with them [2–4]. Individual ion channel proteins are functionally complex, regulating not only the membrane currents that control neuronal excitability and bursting, but also other cellular signaling pathways; as a result, multiple clinical syndromes can result from different mutations in a single ion channel subunit gene. For example, mutations in the SCN1A sodium channel gene can produce phenotypes ranging from generalized epilepsy with febrile seizures (GEFS +, a relatively mild form of childhood epilepsy) to Dravet's syndrome (a severe infantile disorder with medically intractable seizures and severe cognitive impairment) [5,6]. Even among individuals carrying the same mutation in a given gene, the severity of symptoms and their time course of emergence can be highly variable, implicating the action of 'modifier' genes in the individuals' genome. Studies in mouse models indicate that genetic background can be important in determining the clinical expression, or 'penetrance,' of a particular genotype [7,8]. A striking example is the demonstration that co-inheritance of mutations in epilepsy genes can entirely mask one another clinically when they overlap in appropriate brain circuits [9]. The discovery of modifier genes can point the way to new and unexpected targets for antiepileptic drugs.

Considerable progress has been made in understanding the genetic basis of epilepsies associated with severe malformations of brain development, such as lissencephaly, subcortical band heterotopia, periventricular heterotopia, and tuberous sclerosis. For example, it is now known that 70–80% of cases of lissencephaly and periventricular heterotopia are due to mutations in either of two genes, lissencephaly 1 (LIS1) or doublecortin (DCX), and some of the remaining cases are due to mutations in Reelin or Aristaless-related homeobox gene (ARX) [10,11]. Genes mutated in periventricular heterotopias include filamin A [12,13] and ARFGEF2 [14]. Transgenic mouse studies suggest that all of these genes have roles in neuronal migration [10,14–16].

As is true for most common diseases, most epilepsies have a complex genetic basis, in which multiple genes contribute to risk for the disease. One strategy for identifying susceptibility genes for complex diseases is by case-control association studies, using either candidate genes or low-density whole genome scans. These methods have isolated a large number of potential epilepsy susceptibility loci [3,4,17,18]. A more recent approach is high-density, whole genome association analysis [19,20], and a large cohort of patients is currently being recruited and

phenotyped in the US with the goal of performing such a study for epilepsy (http://www.epgp.org).

Whole genome association studies using microarrays of known SNPs are most successful when searching for relatively common gene variants in a population. To find rarer variants, an alternative approach is medical re-sequencing of candidate genes [21–23]. A large-scale, candidate gene re-sequencing project is underway at Baylor College of Medicine to identify novel epilepsy-related variants in 250 ion channel genes [24]. This project will help to define the incidence and profile of ion channel mutations across a broad collection of patients with multiple seizure types and variable degrees of pharmacosensitivity. Another interesting approach that may help identify protective (as opposed to susceptibility) alleles for epilepsy was initiated recently using a large-scale zebrafish mutagenesis screen to identify genes conferring resistance to convulsants [25].

Genetic engineering has made it now routine to recreate mouse models of specific monogenic variants isolated from human epilepsy pedigrees. Such models not only provide insight into mechanisms, such as the preferential impairment of interneurons in sodium channel mutations [7], but also provide an ideal test system for preclinical screening of novel therapeutics. A recent success in this regard has come in the study of seizures mechanisms in tuberous sclerosis (TSC). The products of the TSC 1 and 2 genes, hamartin and tuberin, both regulate a protein kinase called ‘mammalian target of rapamycin’ (mTOR), which in turn acts to promote cell growth [26,27]. Mutations in TSC genes cause over-activity of mTOR and dysregulated cell growth, producing cortical dysplasias composed of giant cells. The mTOR inhibitor rapamycin was tested in a genetically engineered mouse model of TSC and found to improve survival and diminish seizures [28]. A preliminary study suggests that rapamycin may also suppress the development of astrocytomas in human TSC patients [29].

2.1. Future directions

Because epilepsy is such a heterogeneous disorder, progress in understanding its genetic basis would be accelerated by the adoption of precise, standardized clinical phenotypes, including endophenotypes. The use of endophenotypes was pioneered for the study of psychiatric disorders, and include neuropsychological and neuroimaging measures such as fMRI and DTI measures of functional connectivity [30]. Electrophysiological measures have received less study, but have been used in alcoholism [31], schizophrenia [32] and ADHD [33].

Progress in understanding epilepsies of complex genetic origin will require not only the identification of individual susceptibility alleles and analysis of gene–gene interactions, but also the study of gene–environment interactions. Gene–environment interactions are important in the development of acquired as well as idiopathic epilepsies. it has been shown, for example, that family members of individuals with acquired epilepsy are at higher risk of seizures than the general population [34,35], and that genetic background affects kainic acid-induced seizure susceptibility in mice [36]. Another category of gene–environment interactions that will be particularly key to tailoring cures to specific epilepsy syndromes is in individual responsiveness and tolerance to anti-epileptic drugs. Indeed, pharmacogenetic approaches to epilepsy are already beginning to produce clinically important tools in epilepsy therapy. The FDA has recently relabeled the commonly used AED carbamazepine to recommend a newly developed genetic test for risk of severe skin reactions, such as life-threatening toxic epidermal necrolysis and Stevens–Johnson syndrome. The new test identifies the HLA-B* 1502 human leukocyte antigen allele, which occurs almost exclusively in patients with Asian ancestry – a population that comprises around 5% of patients being considered for treatment with carbamazepine [37]. The risk for adverse reactions to carbamazepine is between 1 and 6 per 10,000 new users in countries with mainly white populations, but nearly ten times higher in Asian countries. The

current recommendation is to screen for the allele in Asian patients and not use carbamazepine in those who test positive.

A final important area for future research is the role of epigenetic mechanisms in epilepsy. This topic has been essentially unexplored in epilepsy except in Rett syndrome, a neurodevelopmental disorder with seizures caused by mutations in MeCP2, a gene involved in transcriptional silencing of imprinted genes. However, an epigenetic mechanism has been demonstrated for valproic acid blockade of seizure-induced hippocampal neurogenesis via inhibition of histone deacetylases [38].

3. Epileptogenesis

The term “epileptogenesis” refers to the process by which normal brain tissue is transformed into tissue capable of generating spontaneous seizures [39]. The term is generally considered to include both the initial development of epileptic tissue and the subsequent extension of that tissue during disease progression. There is mounting evidence that the transition from normal to epileptogenic can take as little as minutes to hours or as long as months to years. Hence the concept of a “latent” or “silent” period has been useful to describe this transition. The existence of the latent period suggests that the seizure-prone state results from a progressive series of molecular cellular and circuit changes that evolve over time. If the nature of these changes was known, it should be possible to intervene in the epileptogenic process prior to the onset of seizures and increase the potential for better long-term outcomes. Hence, in recent years there has been a switch in the focus of many laboratories from understanding the biological changes that follow the onset of recurrent seizures to understanding those that precede it.

Most of our information about mechanisms of epileptogenesis has come from animal models. More recently, these studies are being validated in human tissue using cellular and molecular approaches applied to either surgical biopsy material or autopsy samples from epileptic patients. Models currently available for adult-onset epilepsies include rat models of status epilepticus (SE)-induced, post-traumatic, and post-stroke epilepsies [40–42]. Rat models are also available for developmental epilepsies [43,44]. An important observation from these models is that both seizure frequency and latency to emergence of seizures vary depending on the initial insult, suggesting that different precipitating stimuli induce different mechanisms of epileptogenesis. The distribution and severity of structural alterations also varies among different models (hippocampal damage appears milder in traumatic and post-stroke epilepsy than in SE-induced epilepsy, for example), and even among individual animals whose seizures have been induced using a single technique [42].

At the cellular level, epileptogenesis appears to involve a combination of changes in intrinsic neuronal properties, increased excitatory transmission or reduced inhibitory transmission, and enhanced inter-neuronal connectivity. The end result of these is an abnormal predisposition to synchronous activity. At the cellular and molecular levels, a wide array of responses to epileptogenic insults has been observed in animal models and humans [41,45,46]. Temporally, these responses can be organized into three overlapping waves:

1. *First minutes to hours after insult:* the immediate release of neurotransmitters – particularly glutamate – is followed by ion channel activation, calcium influx, up-regulation of protein phosphorylation and other post-translational modification events, activation of immediate early genes, and in some cases excitotoxic injury or cell death (reflected in neuronal and glial swelling, mitochondrial responses, and energy depletion).
2. *Hours to days:* during this intermediate period there is upregulated gene transcription, triggering of inflammatory cascades, glial and vascular responses, and growth factor

expression, and, especially in adult models, neuronal cell death. In adults, during this time there is often a lack of electrographic seizures as recorded by scalp EEGs but interictal activity is commonly observed. In adult animals with electrically induced SE and experimental ischemia, synaptic transmission appears to be suppressed during this period; this observation may help account for the temporary absence of seizures following these insults [47–49].

3. *Weeks to months:* this late period is characterized by remodeling events, including axonal sprouting, synaptogenesis, neurogenesis, gliosis, angiogenesis, circuit reorganization, and increasing predisposition to synchronous activity. Many of these changes continue after the first appearance of seizures and may contribute to disease progression.

A key issue is to understand which of the molecular and cellular alterations described above contribute directly to the development of seizure-prone circuits, and which are ancillary changes. One strategy for identifying key causative changes is to determine whether they are common to multiple animal models. This approach was used in a meta-analysis of global gene expression studies of SE- and TBI-induced epileptogenesis [45]. Interestingly, an especially prominent up-regulation of immune response genes was seen at all time points. A similar result was obtained in a study looking for genes that were simultaneously up- or down-regulated in multiple brain regions after electrically-induced SE [49]. These microarray findings are consistent with previous results in both animal models and humans, which have suggested roles for IL1-b and COX-2 in epileptogenesis [50–54]. Other groups are evaluating changes in synaptic components, including receptor expression and distribution [55–57].

Animal models indicate that mechanisms of epileptogenesis can be developmental stage-specific. Neonatal circuitry differs in many regards from that of adults. For example, GABA receptors are predominantly depolarizing rather than hyperpolarizing, and AMPA and NMDA receptors have different subunit compositions than in the adult (resulting in enhanced excitability) [58]. Consistent with these observations, conventional AEDs have limited efficacy in neonates. Another recent observation is that seizures appear to induce more immature patterns of neuronal neurotransmitter and ion channel and transporter expression in adult animals. This finding has been confirmed in human epileptic tissue. Furthermore, epileptogenesis likely involves synaptogenesis and synaptic “dysplasticity,” which are both robust processes during normal development. It is therefore thought that some forms of epileptogenesis involve seizure-induced reactivation of developmental programs that form new synaptic networks.

If therapeutic interventions are to be targeted at the epileptogenic mechanisms prior to the onset of seizures, it will be essential to have biomarkers for this process. There are few confirmed examples of epileptogenesis in clinical neurology, but two areas that have been studied are post-traumatic epilepsy and febrile seizures of childhood. Imaging has revealed acute alterations that may be associated with later risk of temporal lobe epilepsy, including abnormal hippocampal T2 signals on MRI (at 72 h post-seizure) and medial temporal sclerosis (developing over the subsequent months) [59,60]. A large prospective study is currently underway to determine whether there are causal links between prolonged febrile seizures, imaging and EEG findings, and subsequent temporal lobe epilepsy [61]; demonstration of such links will be necessary to establish imaging and EEG findings as biomarkers for epileptogenesis. Importantly, an animal model of febrile seizures is revealing a similar association between early MRI changes and later increases in neuronal excitability [50].

Other imaging methods have identified tissue changes in patients who are already experiencing seizures, and which might also serve as markers of the epileptogenic state prior to seizure emergence. These methods include fMRI [62], DTI [63], and PET imaging using a tracer of

serotonin synthesis [64]. Functional MRI is also being used to measure basal activity of the brain and has identified resting state networks [65]. Evaluating coincidence of regional activation under baseline and evoked conditions by fMRI and EEG may be particularly helpful in establishing biomarkers for ictal generators in a pre-surgical setting. In addition, abnormalities in regional connectivity may be identified with similar methodologies that could be monitored over time to track the progression of epileptogenesis.

Electrophysiological signals hold special promise as clinically useful biomarkers because they may appear earlier than structural changes observable by current imaging methods, be localized with higher spatial resolution, and offer more insight into potential mechanisms. In addition, they can in theory be monitored continuously over long time periods using chronic recordings or telemetric methods. One class of electrophysiological signals that might serve as a biomarkers of epileptogenesis are “fast ripples.” These are high frequency (100–600 Hz) oscillations that have been recorded interictally with microelectrodes in suspected epileptogenic regions of patients with temporal lobe epilepsy and of kainic acid-treated rats [66,67]. They represent the short-term synchronization of local neuronal ensembles (of less than a cubic mm in size), are spatially stable over time, and may reflect increased density of local chemical synapses or gap junctions due to abnormal circuit organization [68,69]. Similar oscillations have been detected in epilepsy patients during seizures using macroelectrodes [70]. It will be of interest to determine the time course of appearance of fast ripples relative to an initial epileptogenic insult and the onset of seizures.

3.1. Future directions

Understanding epileptogenesis will require analyzing the brain’s responses to epileptogenic insults at the level of individual molecular species, cells and circuits, and monitoring those responses over time. A number of observations suggest that many early, insult-induced alterations in synaptic function resemble ones that occur in response to physiological levels of activity – for example, during long-term potentiation (LTP). Hence, information from research on LTP and other forms of physiological synaptic plasticity is likely to improve our understanding of epilepsy, and may point to new targets for therapeutic intervention. In addition, many new techniques are being developed to explore LTP and synaptic plasticity that will be useful in the study of epileptogenesis. For example, it is possible in animal models to monitor the activity of multiple cells within a discrete area using calcium-sensitive dyes [71] or microelectrode arrays, and the latter have been effectively deployed in humans as well. Finally, we can apply more modern analyses of gene and protein expression to human tissue, both in tissue removed during epilepsy surgery and in archived postmortem tissue. These techniques will enable what should be an important goal of future studies: comparing the responses of different cell types and circuits to epileptogenic insults.

Ultimately, curing epilepsy may require not only halting epileptogenic processes but returning synaptic networks to their pre-epileptic state or by creating a compensatory balance to suppress the excess excitability. Doing so will require a better understanding of the factors that promote the development of seizure-prone circuits, and why some individuals develop seizures after a given type of brain insult while others do not. In addition to genetic and developmental factors, gender, hormonal status, and psychological stressors all have been shown to modulate the development and/or severity of epilepsy [72,73]. The mechanisms through which these factors interact with epileptogenic processes are another topic for future study.

4. Co-morbidities

Epilepsy is rarely a syndrome purely of seizures – rather, it is usually accompanied by other cognitive, behavioral, and emotional changes. These co-morbid conditions have in the past been generally viewed as side effects of seizures, and it has been presumed that they would

disappear once seizures were adequately controlled. This view has been challenged in recent years, in part due to increasing awareness that the expression of co-morbid conditions may precede that of seizures and that these conditions do not uniformly resolve if seizures are fully controlled. Thus, it is increasingly recognized that to improve the quality of life for many people with epilepsy, a "cure" must involve more than stopping or preventing seizures, but also must include ameliorating the cognitive, behavioral, and emotional difficulties that can be an equally or more disabling part of this disorder.

Conditions for which epileptic adults are at increased risk relative to the general population include depression, anxiety, sleep disturbances, cognitive impairment, and psychosis. Of the psychiatric disturbances, depression is the most common (although the rates of psychosis and dementia are the most elevated relative to those seen in the general population) [74–76]. Cognitive impairments include problems with memory, verbal fluency, attention, executive function, and social perception [77–82]. Children with epilepsy show higher rates of ADHD, learning disorders, and behavioral problems, as well as depression and anxiety [83–87]. Reductions in IQ are seen in both childhood and adult epilepsy [88], and mental retardation and autism in Dravet, Lennox–Gastaut, and West syndromes and in epilepsies associated with developmental malformations, Fragile X, and Angelman's syndrome [89–91]. Co-morbid changes can be progressive, both over periods of years and over the course of the life span, and their severity has been correlated with age of onset, seizure frequency and total number of seizures, and increasing age [77,80–82,92]. Higher IQ appears to be protective [82].

The etiologies of behavioral and cognitive impairments in patients with epilepsy are incompletely understood and likely multifactorial. There is little doubt that seizures *per se* can contribute to some co-morbid symptoms. There is good evidence that a seizure can cause cognitive deficits that can last for an hour or more after the seizure has stopped [93], and interictal epileptiform discharges can also be accompanied by cognitive impairment [94,95]. Conversely, cognition in patients with long-standing epilepsy is often, but not always, improved when seizures are successfully controlled by medication or surgery [77]. In addition, animal studies have shown that electrical or chemical induction of seizures causes neural damage and cognitive decline in adult animals [96,97] and disrupts normal brain development in young animals [98,99]. Seizures can also affect cognition indirectly – through sleep disturbance, for example. With regard to psychiatric co-morbidities, social stigma and other negative interpersonal reactions to epilepsy can impact both self-esteem and social relations, which in turn puts patients at higher risk for emotional disturbances [100]. For example, the cognitive and behavioral problems of children with epilepsy are significantly exacerbated if their parents' behavior is destabilized by the child's diagnosis [101].

A second potential source of co-morbidity is anti-epileptic drugs (AEDs), all of which can cause cognitive and psychiatric disturbances. The newer AEDs seem to cause fewer problems than the older ones, but their side effects have also received less systematic study (nine new AEDs have entered the market in the past 15 years). Even with the newer AEDs, significant problems have been observed in some patients. For example, topiramate is associated with relatively high rates of adverse effects, including cognitive impairment, depression and nervousness, and vigabatrin is associated with substantial rates of depression and other psychiatric problems [102–106]. Maternal exposure to AEDs during pregnancy can also cause problems in offspring: valproate in particular has been linked to cognitive impairment, developmental delay, and major congenital malformations [107–110].

Finally, epileptic seizures and co-morbid conditions may arise from a common, pre-existing pathology. Genetic defects leading to seizures may also cause other neurological problems, either through a common pathogenic pathway or separate ones. Similarly, stroke and trauma can cause cognitive impairment, mood disturbances, and behavioral problems either together

with seizures or without them, suggesting the possibilities of both common and independent pathways for the development of these symptoms. The possibility of common underlying pathology leading to multiple phenotypes receives support from findings that cognitive and psychiatric problems are evident in many patients prior to their first seizure. Studies of past histories of children newly diagnosed with epilepsy indicate higher than normal rates of ADHD, learning disorders, anxiety, depression, learning disabilities and behavioral problems before their initial presentation with seizures [84,87,101,111–113]. Adults newly diagnosed with epilepsy were found in three different studies to be 1.7- to 7-fold more likely to have a past history of depression [113,114]. Finally, many patients have poor long-term quality-of-life outcomes despite seizure control, suggesting that co-morbid conditions can continue to progress even in the absence of seizures.

Studies in animal models are beginning to provide insights into the cellular and molecular mechanisms underlying the cognitive deficits associated with epilepsy. In adult animals, seizures cause cell death in temporal structures that subserve memory [42,44,98]. In humans, hippocampal neuronal cell death accompanies seizures and predicts the extent of memory loss following seizures [115]. In neonates, seizures interfere with the development of hippocampal dendrites and the maturation of GABAergic and glutaminergic receptors and scaffolding proteins [55–57]. Dendritic loss and/or abnormalities of dendritic development are also seen in humans with epilepsy [116,117] as well as in Down syndrome and other forms of mental retardation [118]. Finally, studies in rodent models of Rett syndrome [119] and TSC [120], and in rats with electrically [121] or chemically [122] induced seizures, suggest that disruption of long-term potentiation and long-term depression also contribute to learning and memory deficits in epilepsy. Indeed, since both learning and epileptogenesis involve long-term changes in glutaminergic and/or GABAergic transmission at individual synapses, it is not surprising that the development of seizures could be accompanied by the appearance of cognitive deficits.

4.1. Future directions

We need to more precisely characterize the full range of comorbidities in patients with epilepsy. Studies to date suggest that different patterns of co-morbidity occur in different epilepsy syndromes, and even within a single syndrome. For example, a study by Hermann et al. [81] suggests that at least two discrete syndromes of cognitive impairment exist within temporal lobe epilepsy, which are distinguished by selective deficits in memory versus executive function (as has also been noted for age-related cognitive impairment in the general population). The spectrum of cognitive and/or psychiatric problems in a given patient also depends on factors such as the location and laterality of an epileptic lesion, and the individual's pattern of speech dominance prior to the onset of epilepsy [79,85]. It will be important to further characterize the sleep disturbances that occur in epilepsy, as well as somatic co-morbidities, which include increased rates of back and neck pain, arthritis, heart disease, and sudden unexpected death [76,123], and to more fully define the side effects produced by different AEDs. A key ingredient in these endeavors will be to increase physician awareness and recognition of co-morbid conditions.

In searching for potential mechanisms, it will be crucial to understand to what extent the cognitive and psychiatric syndromes seen in epileptic individuals resemble or differ from those seen in the general population. Depression, for example, seems to have a different range of symptoms in epileptic than in non-epileptic patients, with up to 71% of clinically depressed epileptic patients showing atypical patterns of symptoms that don't meet criteria for any of the DSM IV categories (but which frequently show a waxing and waning course most closely resembling dysthymia) [124].

Imaging studies have begun to point to specific structural and functional brain abnormalities associated with epileptic co-morbidities [125]. Future work should include longitudinal

analyses: imaging studies in normal children and those with developmental disorders are now showing that analyzing developmental trajectories may be far more useful in defining affected brain regions and circuits than analysis of single time points [126–128]. For example, a particular brain region may appear to under-function in experimental subjects relative to controls at one developmental stage, but over-function at another.

Animal models offer great hope for treatment of epileptic comorbidities, as they will enable characterization of synaptic changes underlying these conditions at the cellular and molecular levels, suggest drug targets, and provide vehicles for testing therapeutics. In examples from other disorders, electrophysiological studies of synaptic deficits in animal models of Down's syndrome and neurofibromatosis type 1 provided novel targets for potential therapeutics. These in turn were tested and shown to alleviate cognitive deficits in the animal models, and now can be further developed for testing in the human conditions [129–131]. Animal models have been reported for seizure-induced learning and memory deficits [122], ADHD [132] and depression [133,134], but additional models should be developed and procedures for generating them standardized across laboratories.

5. New technologies for epilepsy diagnosis and cure

Currently, seizures can be controlled in 50–60% of epilepsy patients by drugs and/or surgery, but challenges remain in curing epilepsy in all patients. These include (1) early identification of patients at risk for intractability, (2) accurately localizing abnormal neural activity prior to seizures in patients with uncontrolled epilepsy, (3) developing novel therapeutics for these medically intractable epilepsies, and (4) increasing the specificity of chemical and surgical treatments for epilepsy to maintain or enhance function and minimize or eliminate side effects. However, recent technological breakthroughs promise to speed progress toward these goals. Here we focus on the areas most relevant to epilepsy and some areas in which clear progress is already underway.

Currently, the EEG is still the primary tool for monitoring ictal and inter-ictal activity in humans. A limitation of the EEG is that it measures field potentials, which represent the summed activity of many thousands of neurons. Much greater sensitivity and spatial resolution can be obtained using microelectrode arrays, which record individual action potentials from a hundred or more neurons simultaneously. In addition, broad-band EEG recordings, analysis of locally-generated field potentials, recordings at higher spatial resolution, and over more prolonged periods (even chronically) will provide additional useful information. There is also ongoing research to develop reliable methods based on EEG and localized field potential recordings for predicting seizures before they occur and devising treatments to prevent the impending seizures. In this regard, significant advances have been made recently deploying microelectrode arrays as components of neuromotor prostheses for spinal cord injury patients. The arrays are used to detect activity patterns in the motor cortex associated with intentions for hand movements, which are then translated into an output that controls the movement of a computer cursor or a mechanical hand [135,136]. In epilepsy, one can envision using a similar device to detect pre-seizure electrical activity and normalize it, either through electrical stimulation or local drug delivery. Even more futuristic possibilities are suggested by the recent development of techniques in which optical excitation is used to regulate the activity of neurons that have been targeted with genes expressing light-sensitive ion channels or pumps [137]. This tool allows the activity of individual neurons or circuits to be switched on and off within milliseconds.

Improved drug delivery methods should be enabled by recent developments in gene therapy and nanoparticle technologies. The location-related epilepsies are particularly attractive targets for gene therapy because they arise from circumscribed populations of neurons, and so are

potentially treatable by local injections of gene therapy vectors. The most widely used vector system for gene therapy in the brain is adeno-associated virus (AAV), which can transfect post-mitotic cells (including neurons) with high efficiency and stability and is relatively non-pathogenic [138]. These vectors can be targeted to specific populations of neurons using cell type-specific promoters and/or capsid serotypes. Specific genes that have shown therapeutic effects in animal models of epilepsy include galanin, neuropeptide Y (NPY), and GDNF [139,140]. Nanoparticles offer a new method for delivery into the brain of both gene therapy vectors and traditional pharmaceutical agents [141]. The particles can also be coated with peptides that target them to specific cell types and/or allow them to be internalized by cells, thereby enabling much higher drug concentrations at desired sites of action and minimizing drug exposure of non-targeted cells [142].

Stem cell therapies for epilepsy also look increasingly promising with improved understanding of mechanisms controlling the development of GABAergic interneurons. These neurons help regulate the excitability of the cortex and hippocampus through inhibitory effects on excitatory circuits; hence, increasing their numbers might be effective for inhibiting seizure activity. Most GABAergic interneurons in the cortex and hippocampus are derived from progenitors in the median ganglionic eminence (MGE), from whence they migrate to the telencephalon [143]. MGE cells grafted into a single location in neonatal mouse brain were shown to migrate widely throughout the cortex and differentiate into GABA-expressing interneurons [144]. In this regard, MGE cells may have more therapeutic potential than neural or embryonic stem cells, which typically remain clustered near the transplantation site and whose developmental fates seem less predictable. Enhanced levels of GABA-mediated inhibition were observed in the regions containing the transplanted MGE cells in normal hosts, but the effects of these cells in rodent epilepsy models remain to be determined. In another transplantation approach, embryonic stem cells engineered to release the inhibitory neuromodulator adenosine suppressed seizures in a rat kindling model [131].

5.1. Future directions

Much of our future regarding nanotechnology, implantable devices, and delivery of stem cell or molecular therapies will depend on our bridging biology with materials and energy science in order to access the brain safely with tissue-compatible sensors to provide physicians with constant electrical and biochemical data for analysis. For example, using available field effect transistors shrunk to less than 100 nm in size, investigators can place a biofilm over the transistor and measure pH, electrolytes, or other variables of interest from any location desired (including individual neurons or astrocytes).

6. Final thoughts

Significant progress has been made during the past decade in understanding the causes and mechanisms responsible for numerous types of epilepsy. Due to space limitation for this review we were unable to discuss all of the discoveries made. However, we have attempted to highlight areas of intense investigation and provide examples of the work that has been done.

With the completion of the human genome project and the development of so many tools in molecular genetics, it is perhaps not so surprising how far we have come in such a short time in identifying epilepsy genes. The challenges for the future will be to use this information not only for diagnosis but the development of rational treatments. Gene therapy is clearly an important long-term approach, but in the meantime an understanding of epileptogenic mechanisms arising from gene mutations could provide “downstream” targets for therapy development. Mouse models will be central in screening new treatments. Numerous candidate mechanisms have also been identified for the acquired epilepsies. Understanding which of

these are necessary and sufficient to produce epilepsy should lead to interventions that will stop the development and progression of these seizure disorders.

One area in which we still have much to learn is that of epilepsy co-morbidities – especially cognitive disabilities. The application of recent advances in psychology and neuroimaging, as well as new knowledge concerning the fundamental mechanisms that underlie learning and memory, will provide much needed information in this area.

Based on all of these recent advances and the dedication of a highly diversified clinical and basic research community there is every reason to be hopeful that new therapies or even cures for epilepsy will become available in the next decade.

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