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Can epilepsy be prevented?

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Abstract

The development of epilepsy may be related to genetic and epigenetic factors often in combination with non-genetically determined structural brain abnormalities. Prevention of epileptogenesis (i.e., antiepileptogenic therapy) as well as suppression of seizures (i.e., antiepileptic therapy) is important for complete control of epilepsy. In this article, we will present recent advance to accomplish the goal in an age- and sex-specific fashion.

A number of causes are suggested in epilepsy including pathological lesions in the brain and genetic mutations. On the other hand, an initial precipitating insult (IPI), such as febrile status epilepticus, can play an important role for development of epilepsy in some patients. For instance, in temporal lobe epilepsy, a history of febrile status epilepticus during early childhood is frequently documented although the cause and effect relation is not clear. Epileptogenesis is defined as the process of forming a focus capable of generating spontaneous seizures[1], may progress at times and become a permanent epileptic state, often after latent period.

For complete control of epilepsy, clinical treatments should aim at prevention of epilepsy and its neurodegenerative changes (antiepileptogenic therapy) as well as control of seizures (antiepileptic therapy). Antiepileptogenic therapies include suppression of epileptogenesis during latent period after the IPI, prevention of seizure-induced modification after the onset of epilepsy (e.g., reduction in seizure frequency and duration), reversal of pathology, prevention and improvement of epilepsy-related co-morbidity and finally cure of disorder.[1]

PATHOLOGICAL BASIS OF EPILEPTOGENESIS

Numerous neurodegenerative changes participate in epileptogenesis at different phases.[2] In adult rodents model of status epilepticus, neuronal cell death are initiated immediate after the IPI (within hours to days), gliosis, neurogenesis, reorganization of extracellular matrix and inflammatory process (within 10 days), and mossy fiber sprouting and dendritic plasticity follow (from 10 days to 30 days). Changes in specific gene expression also occur throughout this period. Finally, these acute and subacute changes result in persistent functional alteration and associated with chronic state of epilepsy.

Neuronal cell loss is the most commonly observed degenerative changes in the epileptic tissue obtained from human and animal models of epilepsy especially in adulthood. Excitotoxic neuronal cell death during status epilepticus is acutely caused by a cascade involving activation of glutamate-related receptors, cellular depolarization, calcium influx, activation of intracellular signals, oxidative stress/free radical formation and activation of apoptotic pathways such as caspase activity.[3]

Gliosis is another pathologic hallmark of epileptic tissue. Activated astrocytes and microglia play important roles in neuronal hyperexcitability and epileptogenesis by increasing extracellular potassium and glutamate and by producing chronic inflammatory state in the epileptic focus.[4]

INFLUENCE OF AGE AND SEX ON EPILEPTOGENESIS

Factors influencing on epileptogenesis after the precipitating insults have been suggested and possibly includes age and sex differences as well as specific genetic background and brain pathology.[5] For example, the immature hippocampus is relatively more resistant to the injury after a bout of status epilepticus than the mature hippocampus.[2]

Maturation of neuronal function profiles [such as excitatory (glutamate) and inhibitory

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(γ-aminobutyric acid: GABA)] is normally determined by age and sex.[2] For example, in the substantia nigra, one of the important brain structures for seizure control, GABA receptors mediate depolarizing currents early in life and activate calcium sensitive signaling processes that are vital for neuronal differentiation and brain development.[6] Maturation of GABAA receptor function, i.e., the shift from depolarizing to hyperpolarizing current, is earlier in female than male, resulting in sex-related difference in seizure threshold in immature rats or in the ability to control the spread and duration of seizures.[7,8]

POTENTIAL ANTI-EPILEPTOGENIC THERAPIES

Therapeutic targets for antiepileptogenesis should be based on cellular mechanisms of epileptogenesis and influencing factors described above. Additionally, the effect of anti-epileptogenesis therapy may be stage-dependent. Most of suggested anti-epileptogenic therapies are still pre-clinical (Table 1), but there are some novel approaches that are currently studied with translational studies in humans.

Anti-inflammatory therapies can be an effective approach to control and modify epilepsy.[4] Endogenous inflammatory mediators (cytokines) released from glial cells and neurons mutually activate their transcriptional and non-transcriptional pathways resulting in actions on channels and receptors, glutamate release, neurogenesis, axonal sprouting and angiogenesis. These inflammation-related processes can enhance neuronal excitability and epileptogenesis.[4]

Rapamycin may be a clinically challenging drug. A recent clinical trial with its analogue drugs revealed the suppressive effect on seizure frequency as well as associated brain tumor in tuberous sclerosis.[9] Interestingly, some experimental studies suggested that rapamycin also had an antiepileptogenic and neuroprotective potential.[1]

Gene therapy is another approach. In contrast to conventional antiepileptic drugs targeting specific proteins such as ion channels or receptors, RNA interference therapeutics exploit an endogenous regulatory mechanism of gene expression and thereby are poised to prevent or reverse pathogenetic mechanisms involved in epileptogenesis.[10]

BIOMARKERS OF EPILEPTOGENESIS

Ideally, to prevent epilepsy, we must find available biomarkers for epileptogenesis which represent development and extension tissue capable of generation spontaneous seizures. Potential biomarkers are listed in Table 2. Monitoring these biomarkers may enable the identification of patients with risk factors (e.g., cerebral insult, isolated seizure, febrile status, and gene mutations) who may develop epilepsy to initiate early

Table 1: Potential antiepileptogenic approaches that may need to be age- and sex-specific

Current anti-epileptic drugs
Glutamate inhibitors
Blockade of cytokine release
Hormonotherapy
Immunotherapy
Vaccination after the precipitating insult
Antioxidants
Molecular approaches
Gene therapy
Transplantation
Diets
Exposure to enriched environment
Prevention of the effects produced by a “second hit”
Magnetic/electric stimulation

Table 2: Potential biomarkers for epileptogenesis

Neuroimaging study Hippocampal changes on MRI (T2WI, DTI, MRS) Functional MRI linked to EEG activity Positron emission tomography (FDG, AMT)
EEG Interictal epileptiform discharges (spikes) Focal slowing Fast ripples
Excitability evaluated with TMS
Cognitive markers
Gene expression profiles
Pharmacogenomic profiles
Epigenetic profiles

MRI, magnetic resonance imaging; T2WI, T2 weighted image; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; FDG, ^{18}F-fluorodeoxyglucose; AMT, alpha-methyl-tryptophan; EEG, electroencephalography; TMS, transcranial magnetic stimulation

intervention. In patients who develop epilepsy, the biomarkers may be significant in predicting the patients who may have pharmaco-resistant seizures and/or significant co-morbidities that may benefit from other non-pharmacologic treatments including early surgery.

CONCLUSIONS

Translational studies highlighting the mechanisms of epileptogenesis and antiepileptogenesis together with the establishment of reliable biomarkers are necessary. The recent advance in both clinical and basic science research hold promise that new treatments are on the horizon.

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