The Epilepsies

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DEFINITION

Epilepsy: An episodic disorder of the nervous system arising from the excessive synchronous and sustained discharge of a group of neurons.

Seizures may vary from mild and unnoticeable to full-scale convulsive seizures.
Some Common Symptoms of Epilepsy

- Transient loss of consciousness lasting a few seconds
- Unable reading of signals of audio, video and sense
- Disorientation
- Confusion
- Sudden fear
- Uncontrollable movements of the body
- Loss of consciousness
A patient’’s handwriting

C
Writing

Draw a man

Before PEX

Week 4 of PEX

Week 10 of PEX
Classification of Epileptic Seizures
International League against Epilepsy, 1981

- **Partial Seizures**
  - Simple Partial
  - Complex Partial
  - Partial Evolving to Bilateral Tonic-Clonic

- **Generalized Seizures**
  - Absence
  - Atypical Absence
  - Tonic
  - Clonic
  - Tonic-Clonic
  - Atonic
  - Myoclonic
  - Mixed Forms
Partially: Begin in, and remain localized to a particular brain region. Symptoms determined by site of discharge and degree of spread.

- Simple partial: e.g. Jacksonian motor epilepsy, Jacksonian sensory epilepsy. **Motor cortex:** convulsions, repetitive contractions of muscle groups, loss of control but not of consciousness.

- Complex partial: e.g. psychomotor epilepsy, Temporal lobe epilepsy. **Temporal lobe:** strange, irrelevant behavior which may be violent - of which patient is totally unaware.
Generalised seizures

**Generalized:** involve whole brain
**Grand mal:** Clonic tonic, with loss of consciousness, defecation 大便, micturition 排尿 and salivation often occur, 2-4 min.
**Petit mal or absence:** transient loss of consciousness lasting a few seconds.

**Reticular activating system:** loss of consciousness.
Prevalence Active Epilepsy

- World-wide Prevalence: 1%
- Chinese Prevalence: 0.44%
- 125,000 patients increased in USA annually
- Partial seizures ~60% epilepsy
  - 75-85% due to temporal lobe epilepsy
- $12,000,000,000 cost in USA annually
Famous People with Epilepsy

- Julius Caesar
  - Roman Statesman
  (100-44 B.C.)

- Peter the Great
  - Russian Czar
  (1682-1725)
Famous People with Epilepsy

- Napoleon Bonaparte
  - Emperor of France
  - (1769-1821)
Famous People with Epilepsy

- Vincent van Gogh - Painter (1853-1890)
Famous People with Epilepsy

- Fyodor Dostoevski - Writer (1821-1881) Crime and Punishment
- Lord Byron - Poet (1788-1824)
- Franklin D. Roosevelt
- Charles Dickens
EEG patterns

- Absence seizure: the 3 per second spike wave activity in cortical areas.
FIGURE 16.1 EEG patterns in human epilepsy.

(a) Normal

F: frontal, T: temporal, C: occipital
(b) Generalised seizure (grand mal) — tonic–clonic type

1: normal, 2: tonic wave, 3: clonic wave, 4: post-convulsive coma
(c) Generalised seizure (petit mal) — absence seizure type

The typical 3 per second spike wave activity.
(d) Partial seizure

Do not involve the whole brain.
Normal waves

- α波
- β波
- θ波
- δ波

Epileptic waves

- 脑波
- 尖波
- 脳慢波综合
- 脳慢波综合

spike wave  sharp wave  spike & slow wave complex    sharp & slow wave complex
### Normal brain wave

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Wave</th>
<th>Amplitude</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-3Hz</td>
<td>δ</td>
<td>20-200 μV</td>
<td>Temporal and occipital cortex of adult during sleeping. Children.</td>
</tr>
<tr>
<td>4-7Hz</td>
<td>θ</td>
<td>20-100 μV</td>
<td>Teenage. Temporal and frontal cortex of adult at sleepy and depression.</td>
</tr>
<tr>
<td>8-13Hz</td>
<td>α</td>
<td>20-100 μV</td>
<td>All cortex, especially occipital with eyes closed. Disappeared at eyes open. (α 阻断)</td>
</tr>
<tr>
<td>14-50Hz</td>
<td>β</td>
<td>5-30 μV</td>
<td>Main brain wave during waking. Especially in temporal and frontal cortex.</td>
</tr>
</tbody>
</table>
Epileptic brain waves

1. spike wave, <70ms, 50-150 μV, temporal lobe epilepsy
2. sharp wave, 70ms-200ms, 100-200 μV
3. spike and slow wave complex: one or several spike waves followed by a slow wave, or vice versa. 200--500ms, 100--200 μV
4. sharp and slow wave complex: a sharp wave followed by a slow one. 500-1000ms.
WANTED: SUBJECTS FOR RESEARCH ON BRAIN WAVES AND INTELLIGENCE.

SORRY—IT APPEARS YOUR BRAIN WAVES ARE ALWAYS AT LOW TIDE.
Diagnosis

- A thorough evaluation of patients medical history describing seizure characteristics and frequency.
- Electroencephalograph (EEG):
- Magnetic resonance image (MRI)
ANIMAL MODELS

Generalised:
Electric shock
Chemical convulsants: bicuculline or picrotoxin, pentylenetetrazol. Injected systemically.

Partial
Focal: cobalt, alumina, PTZ, kainic acid: 1-2 ug·kg⁻¹ nuclei
Kindling: electric stimulation. 0.2-1.0 mA, 60 Hz, 1-2 s

Genetic animal
Tottering mice, DBA/2 audiogenic, Senegalese baboon (Papiopapio) photoically-induced
Racine grade

- stage 1: chewing, facial clonus, a series of rapid muscle contractions;
- stage 2: head nodding;
- stage 3: lateral forelimb clonus;
- stage 4: rearing and bilateral forelimb clonus;
- stage 5: rearing and falling.
rearing and falling
tailing
In vitro models

- Tissue model: 70~400μm
- Cell model: culture media without Mg$^{2+}$
<table>
<thead>
<tr>
<th>Human epilepsy</th>
<th>Animal model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple partial (acute)</td>
<td>Penicillin, bicuculine, 马钱子碱</td>
</tr>
<tr>
<td>Complex partial (chronic)</td>
<td>Implant metal ion: Al₂O₃, cobalt, focal cortex frozen</td>
</tr>
<tr>
<td>Complex partial seizure</td>
<td>a kindling (electric and chemical)</td>
</tr>
<tr>
<td></td>
<td>b nuclei microinjection: kainic acid, 破伤风毒素</td>
</tr>
<tr>
<td></td>
<td>c genetic E1 mouse</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>a genetic: baboon, audiogenic seizure mouse, Tottering mouse, Mongolian gerbil</td>
</tr>
<tr>
<td></td>
<td>b maximal electric shock</td>
</tr>
<tr>
<td></td>
<td>c systemic proconvulsants: PTZ, penicillin, picrotoxin, allylglycine (烯丙基甘氨酸), 马钱子碱, anti-B6 drugs (如：硫代半二肼酰)</td>
</tr>
<tr>
<td>Generalized absence</td>
<td>Thalamus stimulus, bilateral cortex (penicillin, cobalt), systemically given penicillin, g-羟基丁酸, intravenous infusion of opioid drugs, THIP, genetic models</td>
</tr>
</tbody>
</table>

THIP (4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol)
Kindling model

- Electrodes are implanted in limbic structure or other brain region. sub-clonic electric stimulations (0.2-1.0mA, 60Hz, 1-2 s, square wave) are repeatedly given. Motor epilepsy will be induced after 3 weeks.

- Stimulated regions: amygdala, hippocampus, pericortex, entorhinal cortex, olfactory bulb (嗅球), septum (隔), caudate nucleus and neocortex.

- Experimental animals: frog, Mongolian gerbil, mouse, rat, rabbit, cat, dog, monkey, and baboon.

- The most common: rat amygdala electric kindling model
PROCESS OF ELECTRIC STIMULATION

- Electric stimulation with enough amplitude could induce epileptic spiking at the beginning. It is called ‘after discharges’. No or less behavior response is detected.
- With increased times of stimulations, time and amplitude of ‘after discharges’ increase and ‘after discharge threshold’(ADT) decrease gradually.
- After about 15 stimulations, the rat is easy to get tonic-clonic convolution.
- Once the rat is kindled completely, one stimulation could induced similar convolution. The high sensitivity could last for months.
- If kindling stimulation is kept being given, the severity of motor convolution will increase to:
  - Stage 6, multiple falling,
  - Stage 7, seizure with running(running fits),
  - Stage 8, many one symptom above plus tonic.
- After about 250 stimulations, the rat could get seizure automatically. It suggests that kindling could mimic the happening of epilepsy.
Rat amygdala electric kindling model: the most common model for human ‘complex partial evolving to bilateral tonic-clonic’

① the efficacy of anticonvulsants for both are similar.

② the pathological changes of both are similar. Selective death of neurons and sprouting of mossy fiber happen in rat hippocampus with 150 kindling stimulation.

③ kindling could lead to automatically recurrently seizure of convulsion.
Kainic acid model (KA)

- KA is agonist of glutamate receptor. Acute seizure could be induced by KA 8-12mg·kg⁻¹ ip/sc or brain microinjection of 1-2ug in rat.

- Process of convulsion:
  - 5min, staring, chewing, nodding, wet dog shaking.
  - 30min, facial clonus, then lateral and bilateral limb clonus, clonus of whole body, imbalance, falling.
  - 2~3hrs, convulsion decreases.
  - 1~2days, ‘recovery’
  - 10days later, more than half animals get convulsion again.
  - 10~30days the convulsion is called chronic convulsion.

ip: intraperitoneal       sc: subcutaneous       FEATURE
CHEMICAL PROCONVULSVANTS

- Advantage: inhibitors exist as research tool.

- Common proconvulsants: anti-GABAergic, cholinergic, glutamatergic drugs.
  - Bicuculline, antagonist of GABA (A) receptor
  - Allylglycine, inhibit GAD, synthase of GABA
  - Pilocarpine, Choline-like drug
  - Kainic acid, agonist of glutamate receptor and neural toxin. CCP and MK-801, antagonists of NMDA receptor, could block epileptic discharge and neuronal damage.

GAD, glutamic acid decarboxylase 谷氨酸脱羧酶
Microinjection of penicillin into rat brain hippocampus

e.g. P3R/L2H3.7
Tissue model

- Tissue selected: convulsion-sensitive regions like hippocampus, cortex, amygdala, thalamus. 70~400um thickness.
- advantage:
  - Good stability of electric recording. No effects of breath and blood pressure;
  - Easy to handle under microscope;
  - Easy to control experimental condition: ion concentration, drugs with a little bit toxicity.
  - Neuronal circuitry.
- disadvantage:
  - Short living time.
CELL MODEL

- Epileptiform activity is recorded using whole cell clamp.
- Culture without Mg²⁺: 3 hours, 95% neurons, epileptiform discharge. After Mg²⁺ is removed, neurons still keep epileptiform discharge until death.
- The pathway is mediated by NMDA receptor and Ca²⁺
  - Decreasing calcium concentration, or adding BAPTA block discharge.
  - APV和MK-801, antagonists of NMDA receptor, block discharge.
PREDICTIVE VALUE OF
ANIMAL MODELS

PTZ----absence seizures
Maximal electroshock----tonic-clonic seizures

Epileptogenesis
Seizure

Drugs: increase GABA function or block
NMDA receptors
### Table 16.1  Comparison of the experimental and clinical activities of established antiepileptic drugs

<table>
<thead>
<tr>
<th></th>
<th>Activity against convulsions induced by</th>
<th>Effectiveness clinically in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Electroshock</td>
<td>Pentylene tetrazol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Na valproate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>(+)</td>
<td>++</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

**Notes:**
The data for the experimental studies gives a semi-quantitative guide to relative activities based on $ED_{50}$ values, i.e. ++ = active, + = some effect, – = not active at non-toxic doses. Clinical comparisons are not related to recommended doses but simply indicate whether a drug is effective (+) or not (–). Generally, drugs that are to be used clinically to control tonic–clonic seizures control electroshock but not pentylene tetrazol-induced convulsions in rats and mice, whilst the converse applies to drugs effective in absence seizures. Na valproate is effective in both experimental models and is used in both clinical conditions, although in all cases higher doses have to be used than for any other drug.

**Phenytoin:** 苯妥英  
**Carbamazepine:** 卡巴咪嗪  
**Phenobarbitone:** 本巴比妥  
**Na valproate:** 丙戊酸钠  
**Clonazepam:** 氯硝安定  
**Ethosuximide:** 乙琥胺
CAUSE AND PATHOLOGY

Cause: intense neuronal activation, lower epileptic threshold

Neuropathology: focal lesions
Congenital malformations, Infarcts, Tumours, Cysts, Inflections, Huntington’s Chorea, Alzheimer’s disease

Genetic basis: juvenile myoclonic epilepsy, childhood absence epilepsy
Generalized epilepsy with febrile seizures: SCNIB(Na+ channel beta 1 subunit gene)
Benign familial neonatal convulsions: K channel
Autosomal dominant epilepsy: CHRNA4(Neuronal acetylcholine receptor protein, alpha-4 chain)
What Causes Epilepsy?

- In over 70% of cases, no cause for epilepsy has been identified.
- The other 30% can result from many other possibilities.
“Traditional” Risk Factors

- Genetic conditions
- Head injuries
- Lack of oxygen during birth
- Lead poisoning
- Severe Infections (Meningitis and Encephalitis)
- Problems during development of the brain

- Post-surgical seizures
  - Stroke
- Multiple Sclerosis
  - Alzheimer
- Neuro Infection
- Alcohol & Drugs
- Cerebral Tumor
Epileptic Syndromes

• Genetic / Idiopathic
  – Examples:
    • Petit Mal Epilepsy
    • Grand Mal Epilepsy
    • Juvenile Myoclonic Epilepsy
    • Rolanic Epilepsy

• Acquired
  – Examples
    • Temporal Lobe Epilepsy
    • Frontal Lobe Epilepsy
    • Lennox-Gastaut Syndrome
Single locus gene mutations causing spike-wave epilepsy in the mouse

无生气的 摇摇晃晃的
Main brain regions related to epilepsy

- amygdala
- hippocampus
- Pre-pericortex
- Brain stem reticular structure

- Facial clonus, limb clonus
- Tonic seizure, running clonus, seizure and spreading
海马 hippocampus

- Septal Pole
- Temporal Pole
- Dentate Gyrus
- CA1
Separable and independent seizure-generating circuits exist in forebrain and hindbrain.

Intricate and complex interconnections, especially in the ventral midbrain region.

SN: substantia nigra; AT: area tempestas.
Pathology of excitatory neurotoxicity

- Neuronal loss
  - Pyramidal cells
  - Dentate granule cells
  - Inhibitory interneurons

- Neuronal damage
  - Reduced arborization of dendritic tree
  - Reduced GABA receptors
  - Reduced NMDA receptors

- Neuroplasticity
  - Upregulation of NMDA receptors
  - Downregulation of GABA receptors
  - Sprouting of dentate granule cell axon
A. 非癫痫

B. 癫痫

胶质

正常神经元末梢

对称性突触末梢

癫痫灶内锥体细胞上抑制性突触减少，胶质细胞增生

AS

OL

MG
Mesial Temporal Sclerosis
Pathophysiology of Focal Epilepsy

- Partial seizures generally are associated with a focal structural lesion
- Example: Low grade glioma of left temporal lobe
Response to neuronal injury

A → Injury → Glutamate → B → Plasticity → C

GABA

NMDA sites
TCP sites
GABA sites
Changes in excitatory neurotransmitter receptors in mesial temporal sclerosis

![Graph showing receptor binding levels for TLE patients. The x-axis represents TLE patient numbers from 1 to 8, and the y-axis represents receptor binding levels as a percentage of autopsy control. The graph compares NMDA recognition site, Glycine receptor, and PCP receptor binding.]
Seizure of Right Mesial Temporal Onset
DEVELOPMENT OF AN EPILEPTIC SEIZURE

EEG: electroencephalogram
EPSP: excitatory postsynaptic potential
PDS: paroxysmal depolarizing shift
FIGURE 16.2 Electrophysiological events in the development of an epileptic focus and EEG interictal spike.

IA

Small depolarization

II A

Presynaptic neuron

IB

Larger depolarization

II B

Paroxysmal depolarizing shift (PDS)

A burst of spikes

Postsynaptic neuron
Bicuculline-induced seizure.
Bicuculline: GABA antagonist.
Mechanisms of neuronal excitability

- Voltage sensitive Na\(^+\) channels
- Voltage sensitive K\(^+\) channels
- Receptor-ion channel complexes
  - GABA-Cl\(^-\) channel complex
  - Excitatory amino acid receptor-cation
    - Glutamate
    - Aspartate channel complexes
Sodium Channel

1. Resting (closed)
2. Activated (open)
3. Inactivated (closed)
Action Potential

Sodium potential, depolarization
Neuronal membrane

- Intracellular charge
- Membrane potential over time
- Extracellular charge
- Sodium (Na+), potassium (K+), chloride (Cl−), calcium (Ca^{2+}), and anion (A−) ions

Diagram showing changes in membrane potential and ion concentrations.
Neuron

Na⁺ 外 140 mM，内 10 mM
Ca²⁺ 外 2 mM，内 0.001 mM
K⁺ 外 4 mM，内 140 mM
Cl⁻ 外 140 mM，内 15 mM
<table>
<thead>
<tr>
<th>Ion</th>
<th>Charge</th>
<th>Direction of passive flux</th>
<th>Current generated</th>
<th>Effect on membrane potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>Positive</td>
<td>Inward</td>
<td>Inward</td>
<td>Depolarization</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Positive</td>
<td>Inward</td>
<td>Inward</td>
<td>Depolarization</td>
</tr>
<tr>
<td>K⁺</td>
<td>Positive</td>
<td>Outward</td>
<td>Outward</td>
<td>Repolarization</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>Negative</td>
<td>Inward</td>
<td>Outward</td>
<td>Repolarization</td>
</tr>
</tbody>
</table>
ORIGIN OF FOCAL NEURONS

- Properties of focal neurons
  - Inherent
  - Brain damage

- Reduced inhibition
  - Selective loss of GABA inhibitory interneurons
  - Loss of GABA nerve terminals
  - Reduced GABA uptake

- Increased excitation
  - Supersensitivity to excitatory amino acids.
  - Extensive growth and sprouting of neurons dendrites.
  - Abnormal synaptic transmission
  - Hyperactivity
  - Increase of Na channel number.
Epilepsy and GABA
Postsynaptic potentials

[Graph showing membrane potential over time in milliseconds with labeled points a, b, and c.]
Excitatory amino acid receptors
Calcium Potential

TIME (in milliseconds)

MEMBRANE POTENTIAL

TIME (in milliseconds)
Voltage-sensitive calcium channels:
  L-type, N-type, P/Q-type, T-type

T-type, tiny current or transient

absence epilepsy, petit mal

Ethosuximide, anticonvulsant, block T-type calcium channel
The development of a focus is likely to be determined by one or more of the following:

- Changes in the intrinsic properties and excitability of the focal neuron. Unstable current of neuronal membrane.
- Imbalance of membrane potential-related ions, such as $K^+$, $Na^+$, $Ca^{2+}$, $Mg^{2+}$, $Cl^{-}$.
- A reduction in normal GABA-mediated inhibitory controls.
- An increase in excitatory coupling between neurons.
FIGURE 16.3
Changes in neuronal function required for the development of epileptic seizures.
ORIGIN OF INTERICTAL AND ICTAL SPILKES

FIGURE 16.3
ORIGIN OF ABSENCE SEIZURES

- Originate in the thalamus
- Malfunction of neuronal Ca2+ channels
- Slow-wave discharge
- Symptoms: staring and unresponsiveness
- Animal model: 3Hz stimulation of the intralamina thalamus.
FIGURE 16.4
Changes in the pattern of EEG activity accompanying the development of a full ictal seizure in the anaesthetised rat during the slow intravenous infusion of pentylenetetrazol.
NEUROTRANSMITTERS IN EPILEPTIC ACTIVITY

Changes in neurotransmitters levels and function have been

- Looked for in
  - Human epileptic tissue
  - Animals in which convulsions have been induced experimentally
  - Animals with spontaneous (genetically disposed) epilepsy

- Induced in animals to see how they modify convulsive threshold and intensity.
AMINO ACID MEASUREMENTS

Human studies
➢ Reduced GABA uptake during microdialysis
➢ Reduced GABA levels in the CSF of chronic epileptics
➢ Reduced levels of glutamic acid decarboxylase (GAD)

Animal studies
➢ Loss of GAD staining neurons
➢ Increased release of glutamate
➢ Increased release of Ach

Animals with spontaneous epilepsy
AMINO ACIDS, MANIPULATION (1)

GABA
- Experimentally all GABA antagonists induce convulsions.
  - Bicuculine
  - Picrotoxin

- Blocking GAD promotes convulsion
  - 3-mercaptopropionic acid: substrate competition.
  - Allylglycine: irreversible inhibition
  - Various hydrazides such as semi-carbazide: reduce the action or availability of its co-factor pyridoxal phosphate
AMINO ACIDS, MANIPULATION

GABA

- Augmenting GABA function should provide an anticonvulsant action
- Muscimol: GABA(A) receptor agonists

Table 16.2  Drug augmentation of GABA function

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GABA receptor, agonists</td>
<td>GABA$_A$ — muscimol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABA$_B$ — baclofen</td>
</tr>
<tr>
<td>2</td>
<td>Gabamimetics</td>
<td>Progabide</td>
</tr>
<tr>
<td></td>
<td>Prodrugs</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>3</td>
<td>GABA-t inhibitors</td>
<td>Ethanolamine-$_o$-sulphate (EOS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Na$^+$ valproate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\gamma$ vinyl-GABA (vigabatrin)</td>
</tr>
<tr>
<td>4</td>
<td>Uptake inhibitors</td>
<td>DABB.ACHC</td>
</tr>
<tr>
<td></td>
<td>Neuronal</td>
<td>Nipecotic acid-tiagabine</td>
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<td></td>
<td>Glial</td>
<td>Benzodiazepines</td>
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<td>5</td>
<td>Allosteric enhancement</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>6</td>
<td>Chloride channel openers</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 16.5 The importance of GABA in controlling the development of EEG epileptic spiking.

(a) (b)

(i) (ii) + BICUCULLINE

+ GABA
GABA

- IPSPs 抑制性突触后电位
  - Fast: GABA_A, ligand-gated Cl^- channels
  - Slow: GABA_B, G Protein-coupled receptor

- GABA_A and GABA_C receptors are ligand-gated chloride channels, while GABA_B receptor is G protein-coupled receptor.
The GABAergic System

- Central involvement in epilepsy
- Studies that cite 60-70% less GABA$_{EX}$--Convulsant effect
- Decreased inhibitory function on excitatory system
- Reduction in GABA transport proteins
- GABA release and ion channels
  - Gate Cl$^-$ ions to interior $\rightarrow$ membrane hyperpolarization $\rightarrow$ increase firing threshold (membrane potential?) $\rightarrow$ reduction in the probability of action potential initiation…
  - THUS: neuronal inhibition of NT release (from the positive voltage depolarization)
Neurochemistry of GABA

Glutamate Decarboxylase (+vitamin B6) converts glutamate to GABA, which can be further metabolized by transaminase. Valproic acid and γ-acetylenic GABA are examples of compounds that can inhibit GABA synthesis. Succinic semialdehyde dehydrogenase converts succinic semialdehyde to succinate, which can then be converted to fumarate.
① 谷氨酸脱羧酶和维生素B6辅酶
（-） 烯丙基甘氨酸
（-） semicarbazide
（-） antipyridoxal

突触囊泡

α-酮戊二酸 → 谷氨酸

琥珀酸 → 琥珀酸半醛 → GABA

② GABA转氨酶
（-） valproic acid
（-） γ-acetylenic GABA
（-） γ-乙烯基-GABA
（-） Vigabatrin

GABA_A受体
benzodiazepine barbiturate

③琥珀酸半醛脱氢酶
（-） dipropylacetate
（-） Epilim

GABA转运体
（-） Tiagabin

GABA代谢、作用途径和致抗痫药物
GABA Receptor Agonists

- muscimol
- progabide
- riluzole
- baclofen
- gabapentine (Neurontin)
- vigabatrin
- valproic acid (Depakote)
- tiagabine (Gabitril)
- lamotrigine (Lamictal)
- phenytoin (Dilantin)
- carbamazepine (Tegretol)
- topiramate (Topamax)
GABA Receptor Antagonists

- Flumazenil
- Bicuculline
- Amiphenazole
- Beta-CCB
- Beta-CCE
- Harmaline
- Picrotoxinin
- Picrotin
- Tutin
- Hyenanchin (mellitoxin)
GABA-t inhibitors

Inhibiting GABA transaminase should provide an anticonvulsant action

Animal test
- Ethanolamine-O-sulphate
- Gabaculine
- Aminooxyacetic acid

clinical
- γ-vinyl GABA (vigabatrin)
- Sodium valporate
UPTAKE INHIBITORS

- Blocking GABA transporters should provide an anticonvulsant action
  - tiagabin

RECEPTOR MODULATORS

- Potentiating the action of GABA should provide an anticonvulsant action
  - Benzodiazepine
  - Barbiturates
  - Phenobarbitalone—clinical value
AMINO ACIDS, MANIPULATION (2)

Glutamate
- NMDA receptor antagonists show to be anticonvulsant.
  - AP5
  - AP7
  - felbamate

- Inhibition of glutamate release show to be anticonvulsant
  - lamotrigine
• Glu present [10mM] avg. in most neural cells
  
  much higher than any other excitatory agent.

• High-affinity re-uptake sys. regulates [glu]
  
  Glutamate translocated across the cytoplasmic membrane with $\text{Na}^+$ ionic gradient from ATPase.
ACETHYCHOLINE (Ach)

- Cholinergic agonists, carbachol, induce seizure
- Cholinesterases inhibitors, physostigmine, di-isopropylfluoro-phosphate, induce seizure.
- During seizure, Ach release increases
- Antimuscarinic drugs suppress cholinergic-induced seizures.

- But, antimuscarinic drugs have no clinical effect.
MONOAMINES

NA, 5-HT: a secondary modifying effect?

ADENOSINE

Anticonvulsant?
APPROACHES TO THE CONTROLS OF EPILEPTIC ACTIVITY

- Blocking excitatory voltage-gated Na+ (or possibly Ca2+) channels
- Increasing the opening of inhibitory Cl- channels
- Reducing the release of the excitatory NT, glutamate or its action at NMDA receptors
- Increasing the availability (and release) of the inhibitory NT, GABA by blocking its reuptake or metabolism or activating the GABA receptor either directly or through the benzodiazepine receptor.
FIGURE 16.6 Possible sites of action of antiepileptic drugs. Antiepileptic drugs either directly affect ion channels to reduce Na\(^+\) (1) or increase Cl\(^-\) (2) influx, depress glutamate release (3) or its action through NMDA receptors (4), or potentiate the effect of GABA by reducing its destruction by uptake (5) or metabolism by GABA transaminase (6), acting directly on GABA\(_A\) receptors (7) or potentiating that effect of GABA through an action on benzodiazepine receptors that allosterically alter the GABA\(_A\) site (8). Currently there are no clinically useful drugs that act as glutamate receptor antagonists.
CLINICAL DRUGS

Three types

- **Blocking Na⁺ into cell**: Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topirimate, felbamate, bind inactive Na⁺ channel and keep Na⁺ channel inactive;

- **Gate Ca²⁺ channel**: Ethosuximide selectively treat absence seizure

- **Effect GABA-mediated inhibitory action**: Benzodiazepines, barbiturates, Phenobarbital, Vigabatrin, Tiagabine, Gabapentin. Enhance inhibitory GABAergic neurotransmission, inhibit epileptic seizure
ANTIEPILEPTIC DRUGS
(AEDs)

An effective AED might control seizures and not be too sedative

OLD AEDs
- Phenytoin and carbamazepine
- Ethosuximide
- Barbiturates and benzodiazepines (B & Bs)
- Valproic acid (sodium valproate)
Phenytoin and carbamazepine

---block voltage-dependent sodium channels
---against maximal electroshock-induced seizures and clinically focal and generalized epilepsy.

Ethosuximide

---suppress the transient T-type calcium currents
---against absence seizures only.
Barbiturates and benzodiazepines (B & Bs)

- influence the Cl- channel of the GABA(A) receptor.
- Barbiturates against PTZ-induced seizures.
- Benzodiazepines against partial and generalised tonic-clonic seizures. Clonazepam (1:4 benzodiazepine) against absence seizures, myoclonic jerks, tonic-clonic seizures and status epilepticus.

Valproic acid (sodium valproate)

- inhibit GABA transaminase
- against absence seizure and tonic-clonic seizures and most types of epilepsy.
ANTIEPILEPTIC DRUGS (AEDs)

NEW AEDs
- Lamotrigine
- Vigabatrin (vinyl GABA)
- Tiagabine
- Gabapentin
- Lamotrigine
  - reduce the release of glutamate
  - prolong the inactivation of sodium channels

- Vigabatrin (vinyl GABA)
  - irreversible inhibitor of GABA transaminase.

- Tiagabine
  - block the uptake of GABA

- Gabapentin—an analogue of GABA
  - increase GABA level
  - weaken potentiation of GAD
  - inhibit GABA-t.
OTHER NEW AEDS

- Felbamate
- Zonisamide
- Oxcarbazepine
- Topiramate

- Act on sodium channels
- Act on GABA(A) receptors
FIGURE 16.7
The structure of some established antiepileptic drugs (AEDs) and some newer ones.
<table>
<thead>
<tr>
<th>Established drugs</th>
<th>Use</th>
<th>Mode of action</th>
<th>Comments (half-life, hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDANTOINS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenylhydantoin (phenytoin)</td>
<td>GM (PE)</td>
<td>1</td>
<td>Widely used. Hyperplasia of gums. Anti-folate. Teratogenic. Ineffective in PM (20–80)</td>
</tr>
<tr>
<td>DIBENZAPINES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>GM FE TLE</td>
<td>1</td>
<td>Improves mood. Related to tricyclic antidepressants. Drug of choice in FE (10–20)</td>
</tr>
<tr>
<td>SUCCINIMIDES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>PM (AS)</td>
<td>1</td>
<td>Drug of choice for PM, with Na valproate (20–60)</td>
</tr>
<tr>
<td>BARBITURATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>GM/FE</td>
<td>2</td>
<td>Sedative. Withdrawal fits. Little used (50–100)</td>
</tr>
<tr>
<td>Primidone</td>
<td>GM/PE</td>
<td></td>
<td>Works partly by conversion to phenobarbitone in body</td>
</tr>
<tr>
<td>BENZODIAZEPINES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>SE</td>
<td>8</td>
<td>Given intravenously in SE (&lt;100)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>ME SE</td>
<td></td>
<td>Diazepam largely replaced by clonazepam</td>
</tr>
<tr>
<td>Clobazam</td>
<td>PM</td>
<td></td>
<td>Adjunct to other anti-epileptics. Partly as an anxiolytic</td>
</tr>
<tr>
<td>SHORT-CHAIN FATTY ACIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>GM PM ME</td>
<td>6 also 1 (and 2)</td>
<td>Inhibition of GABA metabolism too slow to explain initial anti-convulsant effect. Increasing use in ME, PM, GM (5–15)</td>
</tr>
<tr>
<td>Newer drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>PE GM (AS)</td>
<td>4 (1)</td>
<td>Fewer side effects (24)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PE GM</td>
<td>?</td>
<td>Excreted unchanged</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>PE (GM)</td>
<td>6</td>
<td>Exacerbates AS (PE)</td>
</tr>
</tbody>
</table>
FIGURE 16.8 Cellular action of phenytoin and carbamazepine.
SUMMARY OF AEDS

- FIGURE 16.6
- No clinically useful drug has been developed using glutamate NMDA antagonist.
- Drugs acting directly on neuronal ions channels are still the most effective AEDS.
OTHER TREATMENTS

Surgery
A clear established focus

Gliosis
Glial cell can protect against seizures
If You Witness a Seizure

Help the person to the floor and cushion the head.

Loosen any clothing around the neck.

Remove any sharp objects.

Turn the person on one side.