

# Phenotyping seizures (epilepsy)

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# Epilepsy

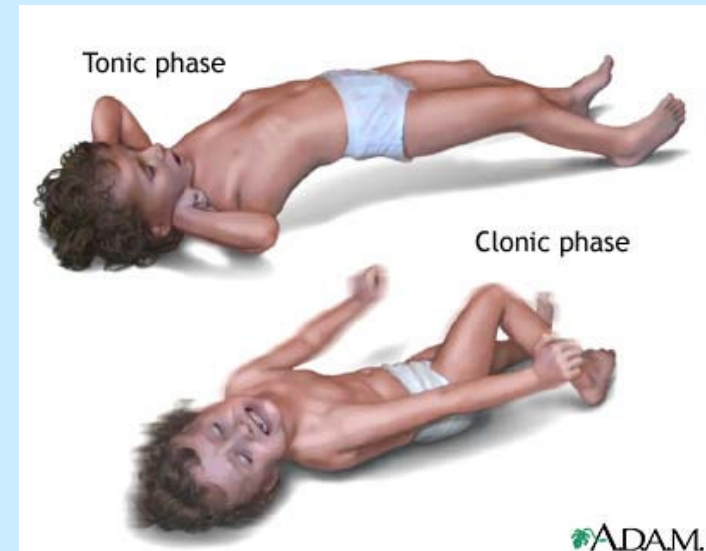
- A group of CNS disorders
- Associated with sudden transient seizure episodes
  - Abnormal motor, sensory, autonomic, and psychic activity
- EEG usually normal
- Different types of epilepsy
  - Secondary (symptomatic) – manifestation of neurodegenerative disease
  - Primary (idiopathic) – patient appears normal
- Genetic forms are rare (account for <1% of all epilepsies)

# Seizure definitions

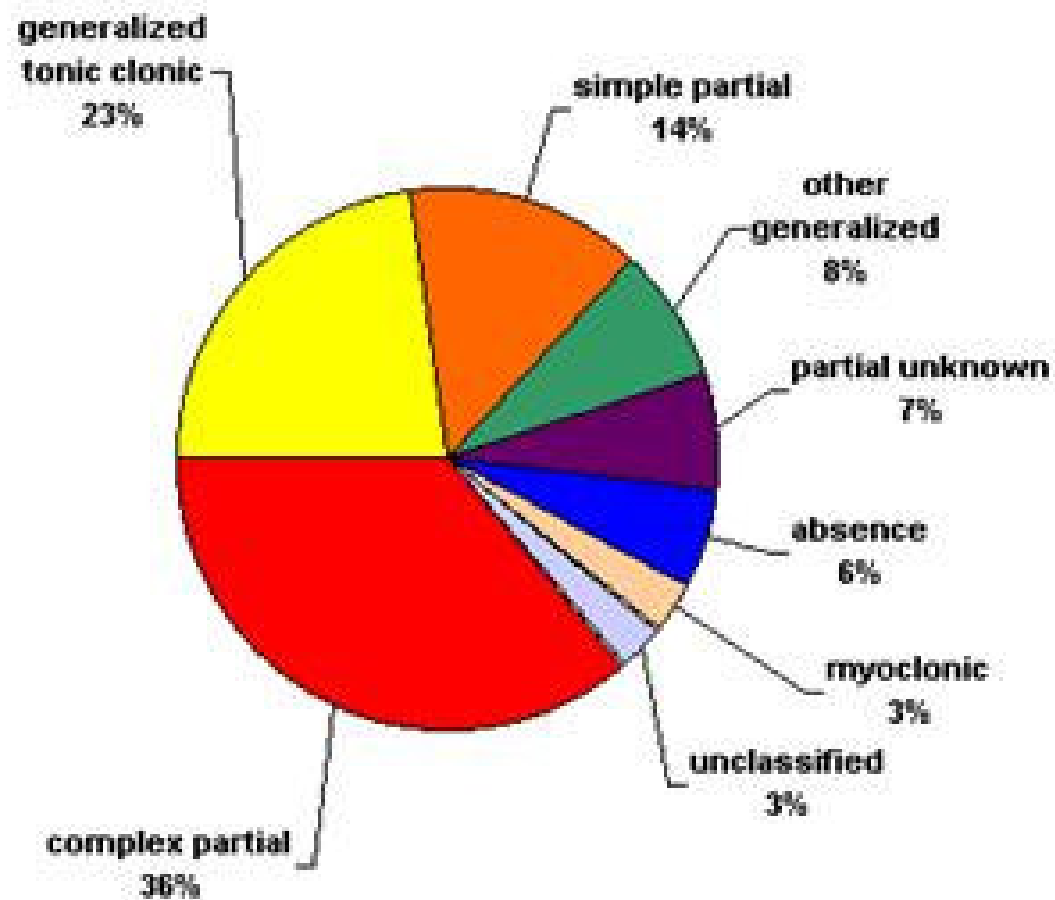
- Clonic seizures consisted of rhythmic contractions of forelimbs and/or hindlimbs
- Tonic seizures consisted of rigid extension of the forelimbs and/or hindlimbs with or without posture loss
- Mortality in both the groups was also assessed over a 30-min period
- An animal was considered dead if the heart was not beating upon manual checkup (the latency of death was reckoned as 1800 s if the animals remained alive after a 30-min observation period)

# Generalized seizures

- **Clonic**
  - Rhythmic muscular jerking
  - loss of consciousness
  - Autonomic involvement
- **Tonic**
  - Extension of arms and legs
  - Loss of consciousness
  - Autonomic involvement



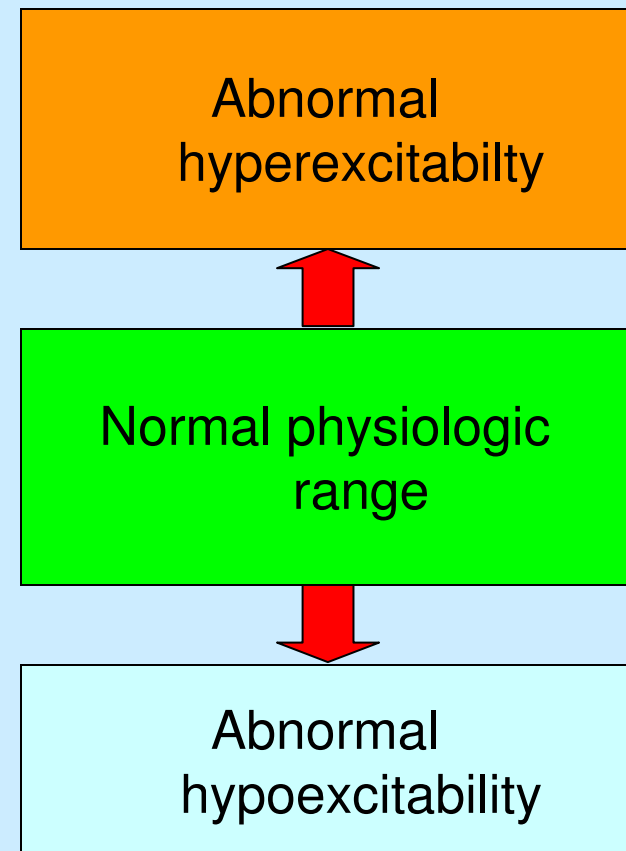
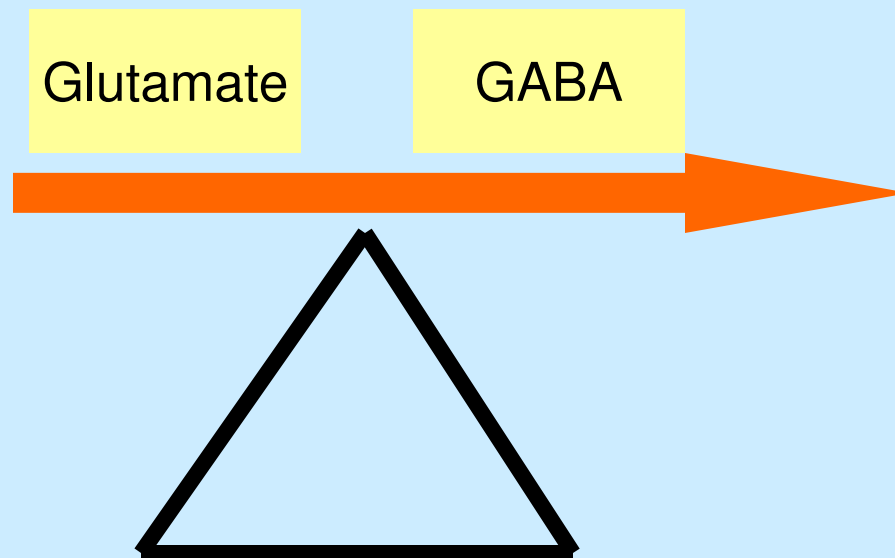
# Types of seizures



# Epilepsy treatment

- Target underlying pathology
  - Most cases are idiopathic
- Seizures associated with elevated neuronal activity
  - Decrease neuronal activity by blocking ion channels, such as  $\text{Na}^+$  or  $\text{Ca}^{2+}$
  - Modulation of ligand-gated ion channels to ↓ Glutamate receptor activity and ↑  $\text{GABA}_A$  receptors

# GABAergic-glutamatergic balance



# Phenotyping epilepsy

## **A common neurological disorder**

- Estimated 10% of the American population experience a seizure in their lifetime
- In addition to its purely neurological aspects, epilepsy has high comorbidity with psychiatric disorders



## **Experimental models of epilepsy**

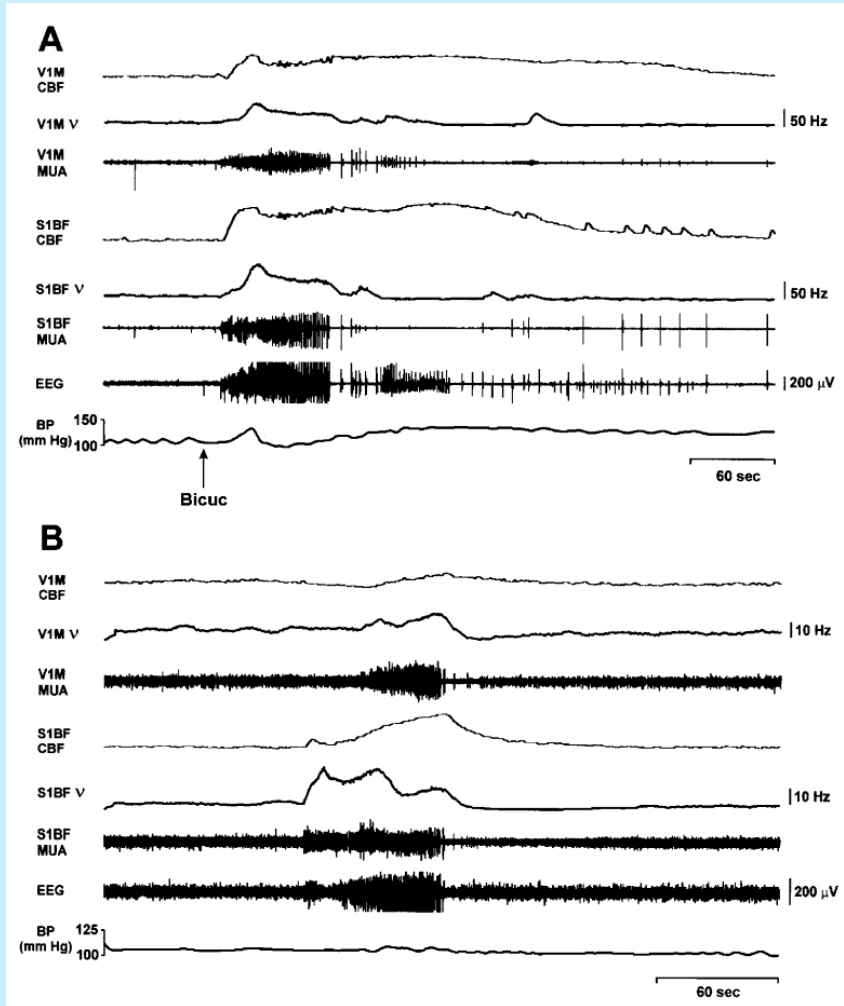
- Chemically-induced, audiogenic, spontaneous and other types of experimental epilepsy
- ≈400 genotypes in the Mouse Genome Informatics database (Jan 2008)



The importance of examining epilepsy phenotypes  
in various animal models



# Neuronal activity during generalized tonic-clonic seizures



Bicuculline-induced (**A**) and spontaneous (**B**) generalized tonic-clonic seizures in WAG/Rij rats

Nersesyan, 2004

# Animal seizure stages

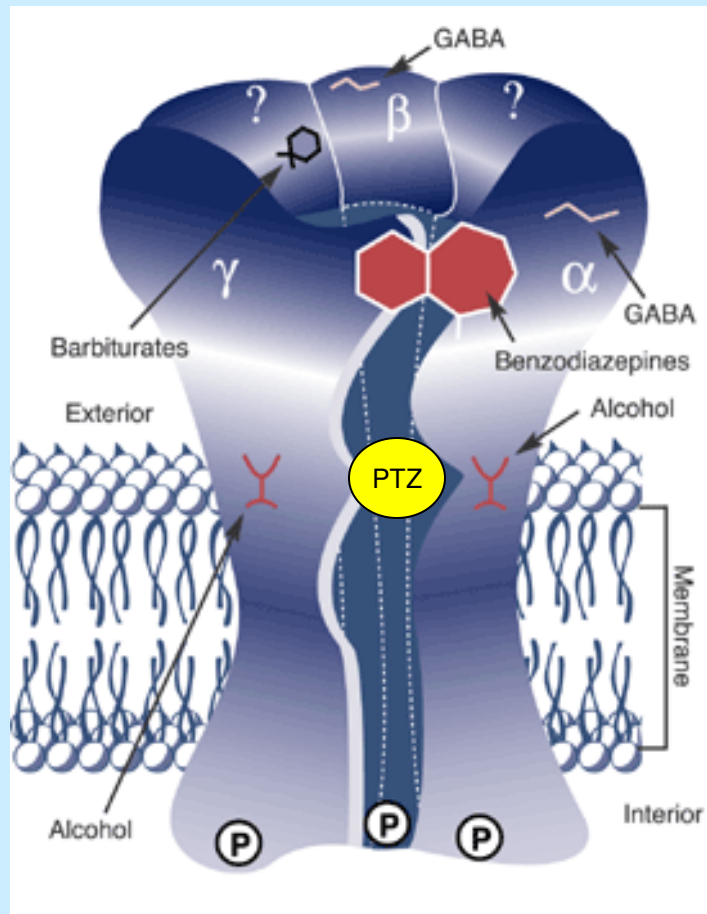
1. Confusion/ tremor/ backward gait
2. Head twitches
3. Individual jerks/jumps
4. Orofacial seizure
5. Clonic seizure
6. Tonic seizure
  - Stage 1
  - Stage 2
7. Death
8. Straub Tail (throughout)

# Racine's seizure activities score (1972)

- 0 = no seizure was observed
- 1 = rhythmic mouth and facial movement
- 2 = rhythmic head nodding
- 3 = forelimb clonus
- 4 = rearing and bilateral forelimb clonus
- 5 = rearing and falling

# Modified Racine's scoring system

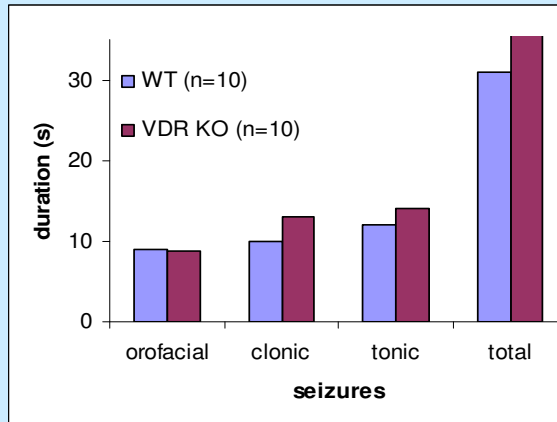
- 0 = no response
- 1 = freezing
- 2 = head nodding or isolated twitches
- 3 = orofacial seizure
- 4 = clonic seizure
- 5 = tonic seizure
- 6 = death



## Pentylenetetrazole (PTZ) – a convulsant blocking GABAergic excitation

- 60-70 mg/kg is standard convulsant dose for mice (assesses the severity of seizures)
- 40-45 mg/kg may be used to assess sensitivity

# Seizures induced by Pentylenetetrazole (70 mg/kg) in VDR<sup>-/-</sup> mice



Kalueff et al. 2006. Neurosci Lett.  
 \*  $P < 0.05$ , & Trend ( $P = 0.05-0.08$ ), *U*-test

Measures	WT ( $n = 10$ )	VDR KO ( $n = 10$ )
Latency to the first twitch (s)	$66.9 \pm 4.5$	$50.4 \pm 4.4^*$
Latency to orofacial seizure (s)	$73.8 \pm 5.3$	$63.2 \pm 4.9$
Latency to clonic seizure (s)	$521 \pm 220$	$179 \pm 74 \&$
Latency to tonic seizure (s)	$701 \pm 246$	$201 \pm 80^*$
Latency to death (s)	$1259 \pm 226$	$429 \pm 167^*$
Mortality rate	4/10	9/10 &
Average Racine's score	$4.9 \pm 0.4$	$5.9 \pm 0.10^*$

# Video 1

# Human epileptic syndromes with animal models

Human condition	Species studied/nature of model
Febrile convulsions	hyperthermia-induced seizures
Absence epilepsies (including childhood, juvenile, myoclonic)	Mice, rat
Temporal lobe epilepsy	Rat/kainic acid, pilocarpine, kindling
Epilepsy due to drug abuse Alcohol Cocaine	ethanol withdrawal cocaine-induced seizures



# Additional animal models for partial and generalized seizures

<b>Seizure type</b>	<b>Model of seizure induction</b>
<b>Partial</b>	<b>Simple partial</b> <b>Focal or topical application of inhibitory amino acid blockers</b> <ul style="list-style-type: none"><li>• Penicillin, Bicuculline, Picrotoxin, Strychnine</li></ul> <b>Cortically implanted metals</b> <ul style="list-style-type: none"><li>• Aluminum, Cobalt, Zinc, Iron</li></ul> <b>Freeze lesion to skull surface/ cryogenic injury</b>
<b>Generalized (tonic, tonic-clonic, and absence models)</b>	<b>Maximal electroshock (MES)</b> <b>Chemical convulsants</b> <b>Glutamate agonists (at maximal dosages)</b> <ul style="list-style-type: none"><li>• NMDA, Kainic acid</li></ul>

Sarkisian, 2001

# Additional animal models for partial and generalized seizures

<b>Generalized (tonic, tonic-clonic, and absence models)</b>	<b>GABA</b> <ul style="list-style-type: none"><li>• Pentylentetrazol (PTZ), Bicuculline, Picrotoxin</li></ul> <b>Glutamic acid decarboxylase (GAD) inhibitors</b> <ul style="list-style-type: none"><li>• Thiosemicarbazide</li></ul> <b>Other agents</b> <ul style="list-style-type: none"><li>• Strychnine</li></ul> <b>Genetic models</b> <ul style="list-style-type: none"><li>• Mice (e.g. weaver, other mutant strains)</li></ul> <b>Miscellaneous animals</b> <ul style="list-style-type: none"><li>• <i>Drosophila</i> mutants, Epileptic dogs</li></ul> <b>Absence models</b> <ul style="list-style-type: none"><li>• systemic low-dose PTZ</li></ul> <b>Genetic models</b> <ul style="list-style-type: none"><li>• WAG/Rij rats, Spontaneous epileptic rat (SER), Stargazer mouse, Tottering mouse</li></ul>
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