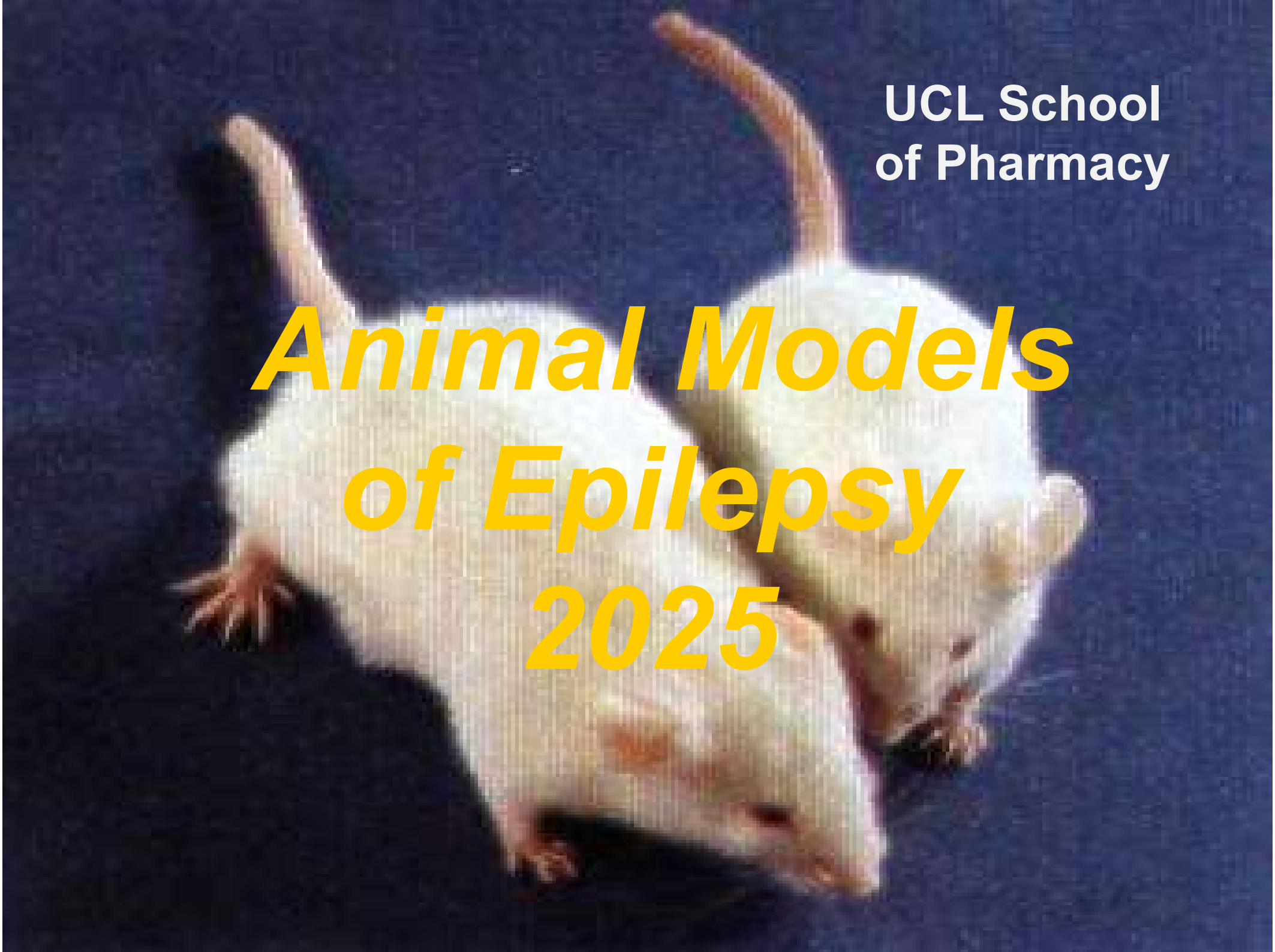

UCL School
of Pharmacy
Animal Models
of Epilepsy
2025

Animal models of epilepsy

- **Epilepsy and its various manifestations** is a complex neurological disorder - the nature of the underlying neuronal abnormality is still poorly understood.

- **Detailed studies on epileptic patients** are difficult or impossible to carry out – therefore, **many different animal models of epilepsy** (both *in vivo* and *in vitro*) that reproduce epileptic seizures, have been developed over the years.

Animal models of epilepsy

- **In experimental animal models, seizures** are induced to model human epilepsy – or with brain slice models – epileptiform activity is induced in neurones by changing the external bathing solution or application of chemoconvulsant drugs or electrical stimuli.

- **Genetic strains of mice (or rats)** are also available that show an epilepsy phenotype. Such studies have provided valuable information on the electrical events underlying a seizure discharge, but the cellular/molecular mechanisms responsible for ***epileptogenesis*** are still unclear.

Animal models of epilepsy

Why do we need animal models?

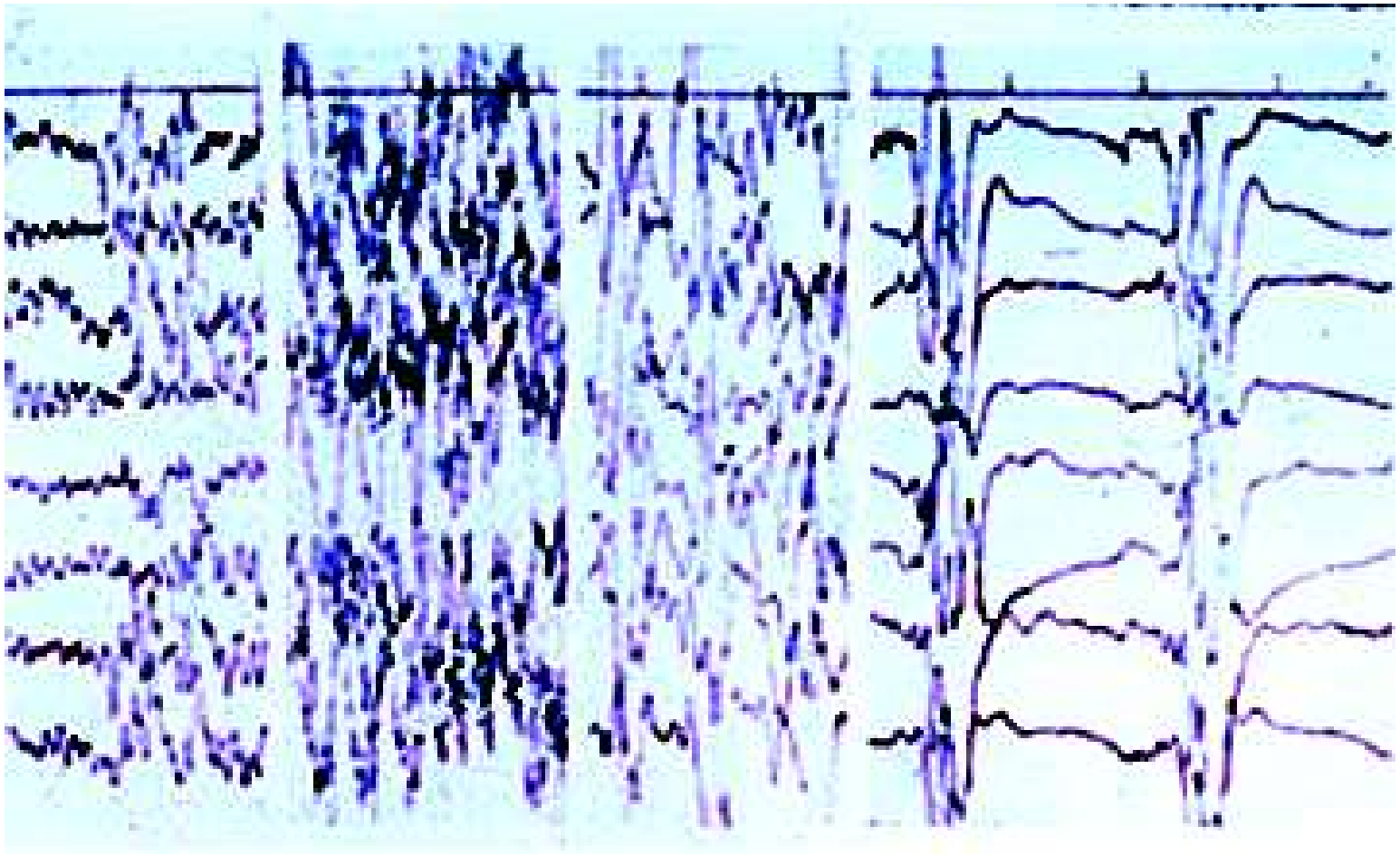
- **Discovery/characterization of new AEDs:** new AEDs are required because there are still epilepsy patients refractory to established drugs. New drugs should have different (more specific), mechanisms of action, fewer side-effects and pharmacokinetic drug-interactions, low teratogenicity and lower rate of relapse after withdrawal compared with old AEDs.
- **Discovery of *antiepileptogenic* drugs:** Following brain insults, morphological/functional changes in the injured area occur over months/years before onset of spontaneous seizures. This latent period offers a therapeutic window for prevention, interruption or reversal of the epileptogenic process.

Animal models of epilepsy

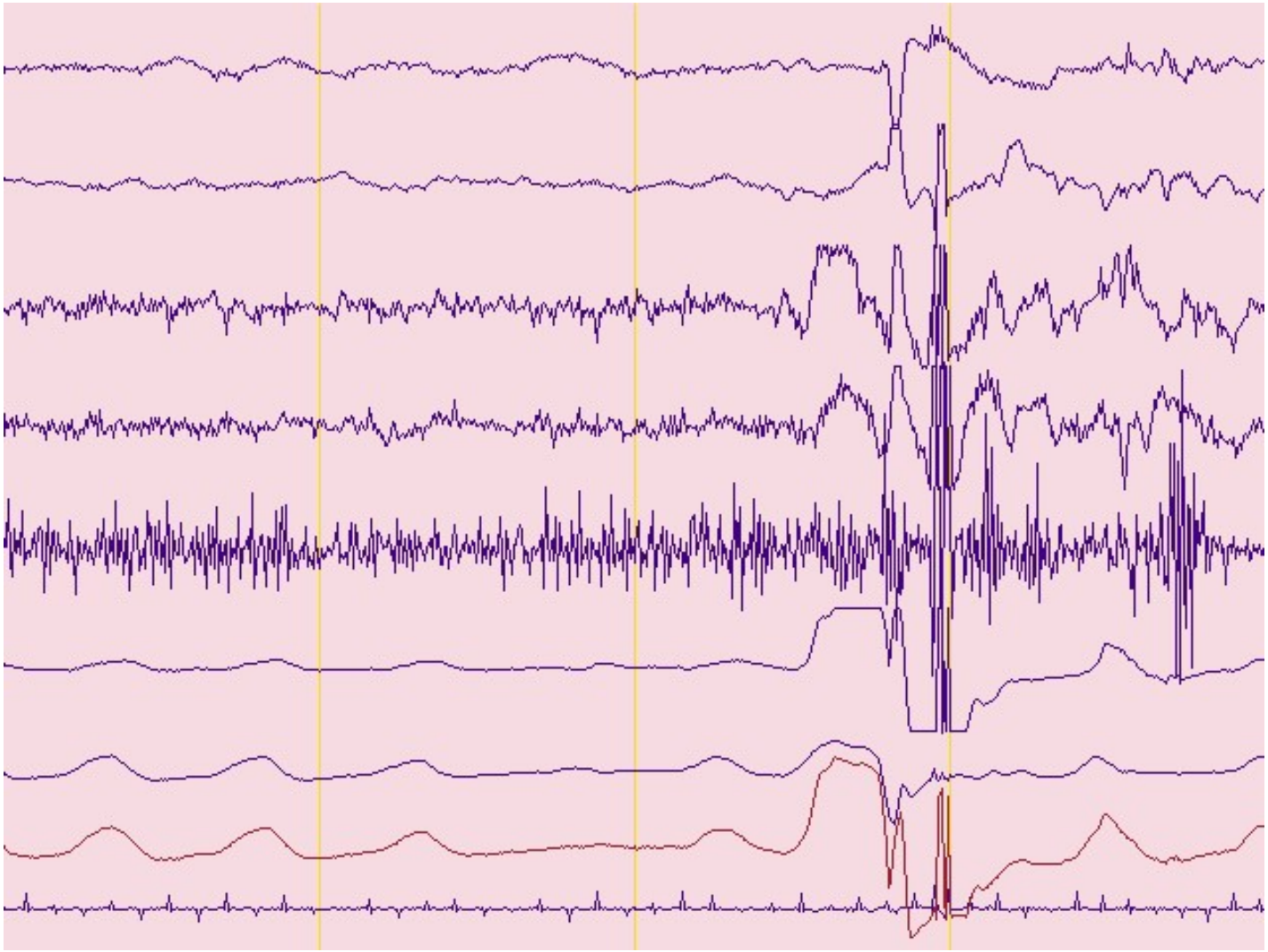
- **Epilepsy is a condition of chronically recurrent spontaneous seizures;** it is a disorder intrinsic to the brain – either **resulting from a 'hereditary tendency'** or after a prior insult (*e.g.* head trauma, stroke, infections, tumours), has caused a portion of the brain to become electrically unstable.

- **The term "animal model of epilepsy" is misleading** – "animal model of a seizure disorder" may be more representative.

- **A seizure (ictus)** is a clinical and behavioural event; - an *in vitro* brain slice model cannot therefore 'suffer from 'epilepsy' in the true sense.



EEG recording showing pattern of brain activity in a human patient during a generalized epileptic seizure.



EEG recording showing *interictal* epileptiform discharges in the brain of a human epilepsy patient.

Animal models of epilepsy

PARTIAL

Simple partial, acute

Topical convulsants:

Penicillin
Bicuculline
Picrotoxin
Strychnine
Cholinergics

Acute electrical stimulation

Brain slices

GENERALIZED

Generalized tonic-clonic

Genetic:

Audiogenic seizures in mice
"Totterer" and *"EL" mice*
Genetically epilepsy-prone rats

Maximal electroshock (MES)

Systemic chemical convulsants:

Leptazol (pentylenetetrazol)
Picrotoxin
Bicuculline
Penicillin
Flurothyl

Models for focal seizures

Application of topical convulsants:

- This attempts to model the focal seizure discharges arising from acute cortical injury -*e.g.* ***trauma, heamatoma***

- A convulsant *e.g.* **penicillin, bicuculline,** or **picrotoxin** is topically applied to an area of exposed rat or cat cortex

- Intracellular recordings made from cortical neurones in such penicillin foci reveal the **paroxysmal depolarizing shift (PDS)**

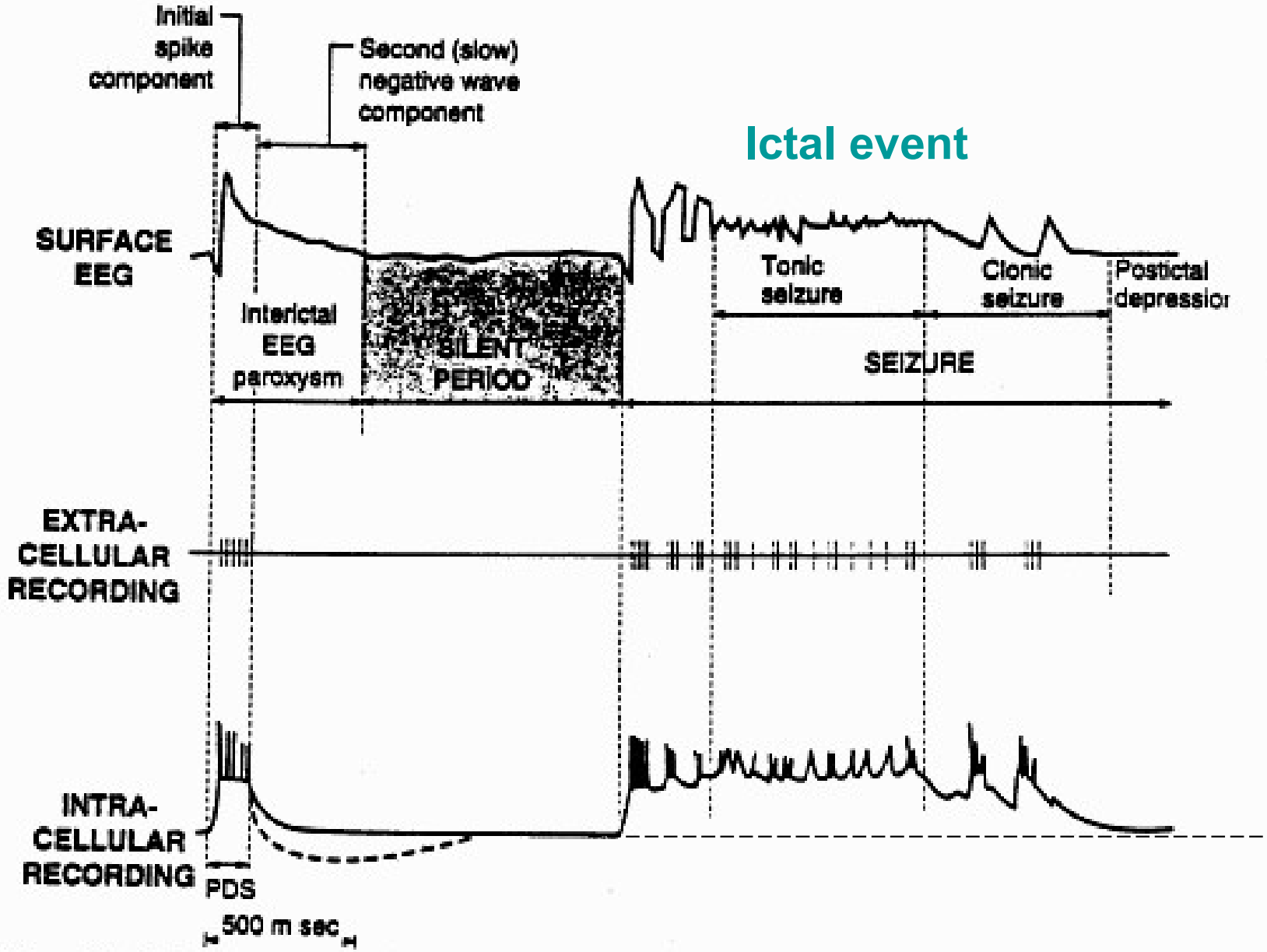


Figure 20–1. Relations among cortical EEG, extracellular, and intracellular recordings in a seizure focus induced by local application of a convulsant agent to mammalian cortex. [Penicillin]

The extracellular recording was made through a high-pass filter. Note the high-frequency firing of the neuron evident in both extracellular and intracellular recording during the paroxysmal depolarization shift (PDS). (Modified from Ayala *et al.*, 1973, with permission.) Brain Research 52 (1973) 1-17

‘Normal’ synaptically-evoked EPSP-fIPSP complex

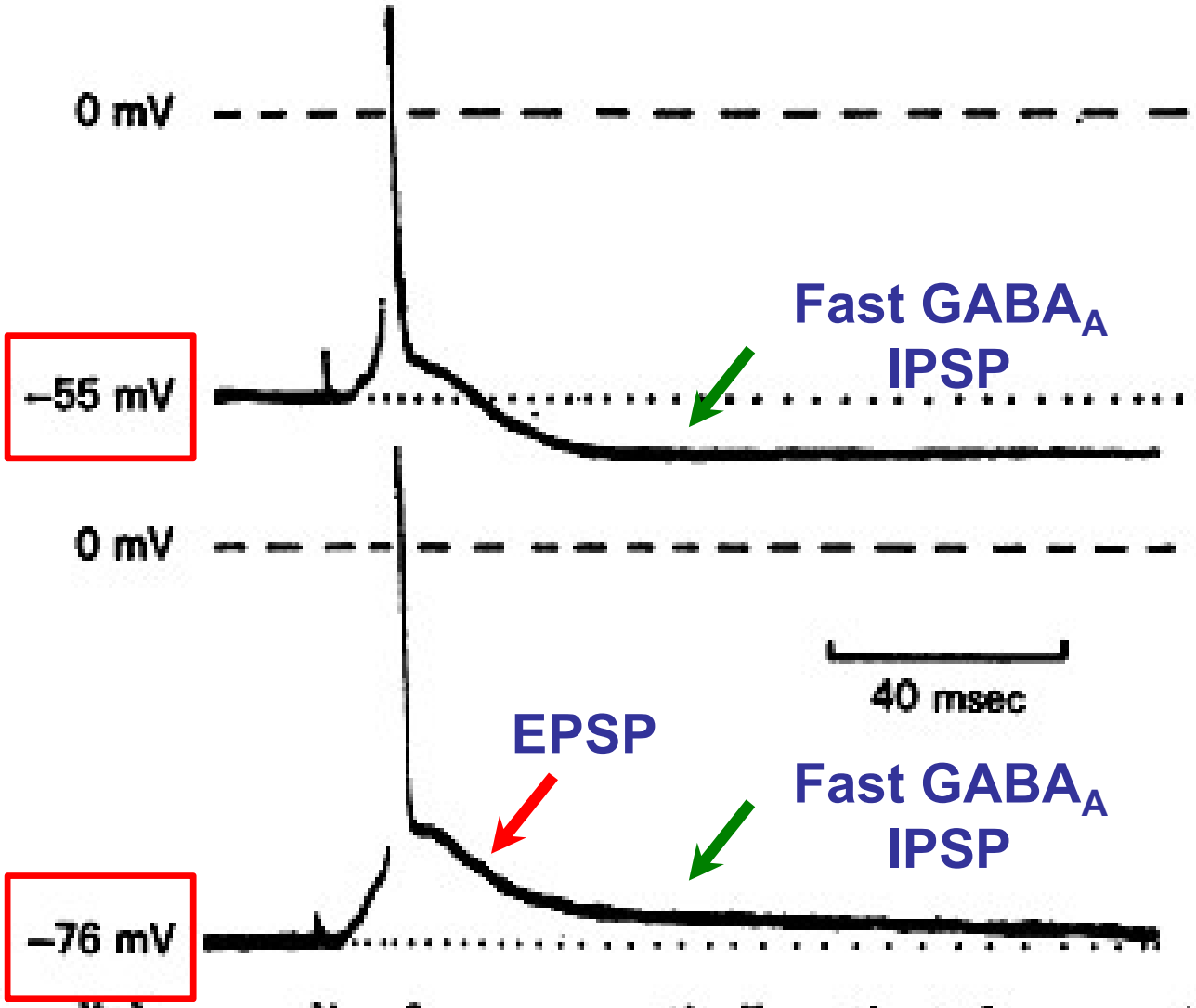


Fig. 1. An intracellular recording from a synaptically activated neurone in the olfactory cortex. The upper trace is a recording on stimulating the l.o.t. immediately after impalement when the membrane potential was — 55 mV.

Synaptically-evoked EPSP-fIPSP/sIPSP complex

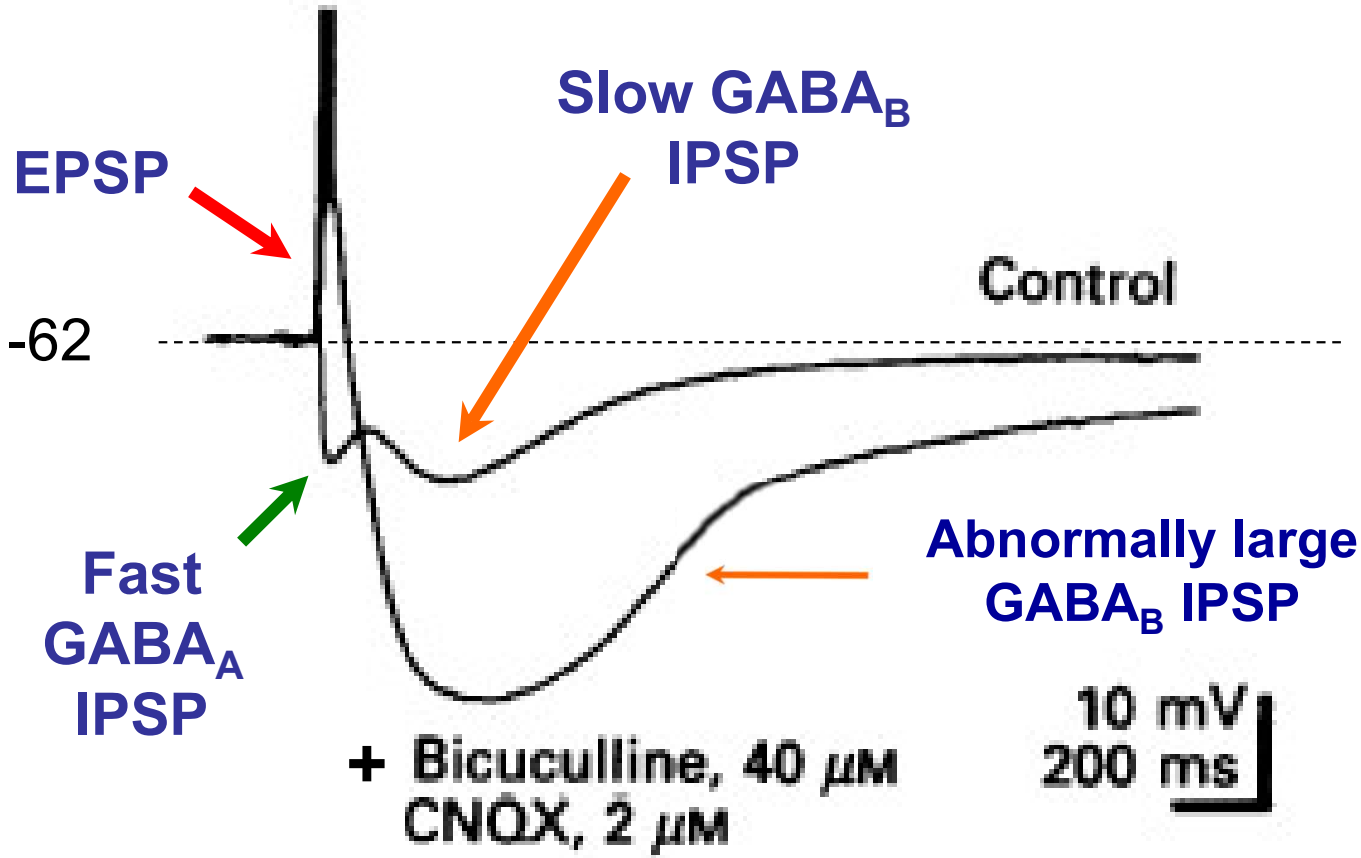
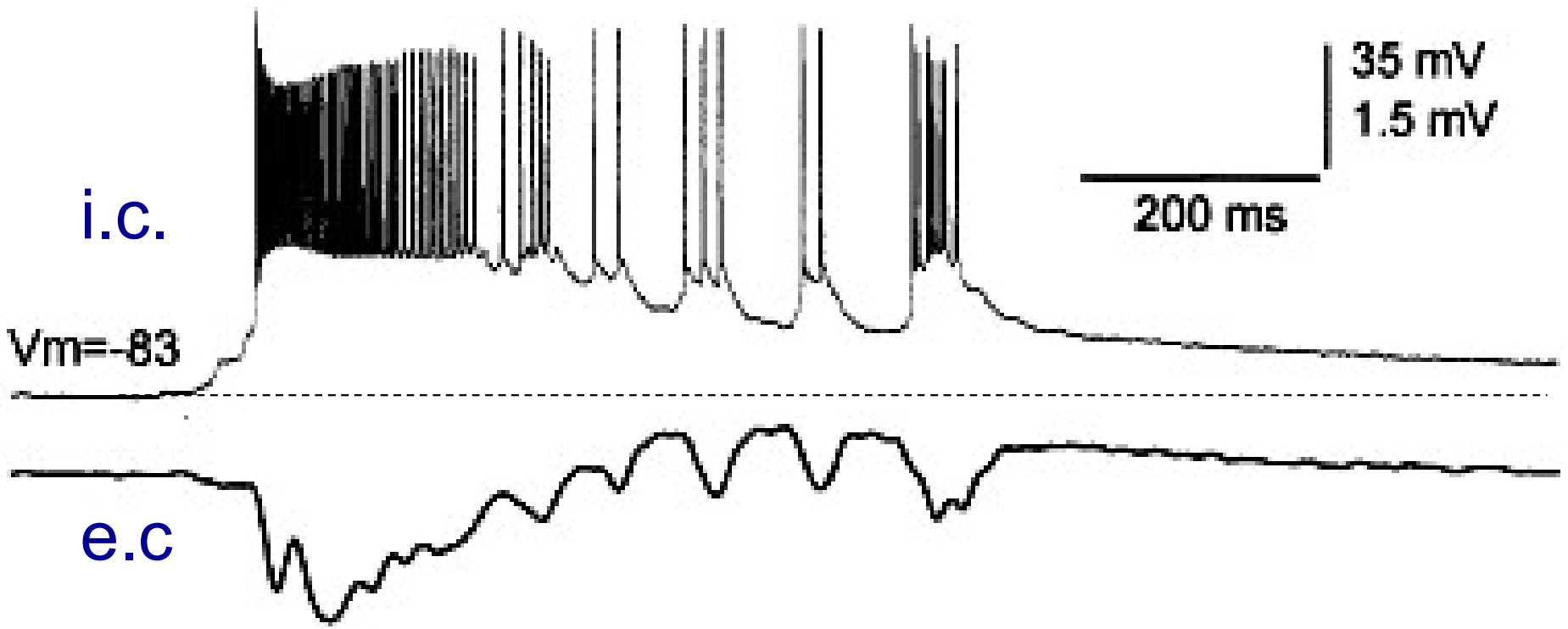


Fig. 3. *A*, the synaptic response of a CA3 cell in control conditions is superimposed on the response of the same cell in the presence of bicuculline (40 μM) and CNQX (2 μM). Note that in bicuculline and CNQX, the early component of the IPSP was blocked, revealing a large EPSP, while the late component of the IPSP was replaced by a paroxysmal inhibitory potential.

Disinhibition in neocortical brain slice neurone



A, representative trace pairs of intracellular (layer V; upper trace) and extracellular (layer III; lower trace) recordings corresponding to spontaneous discharges produced during application of BMI, BMI+CGP35348

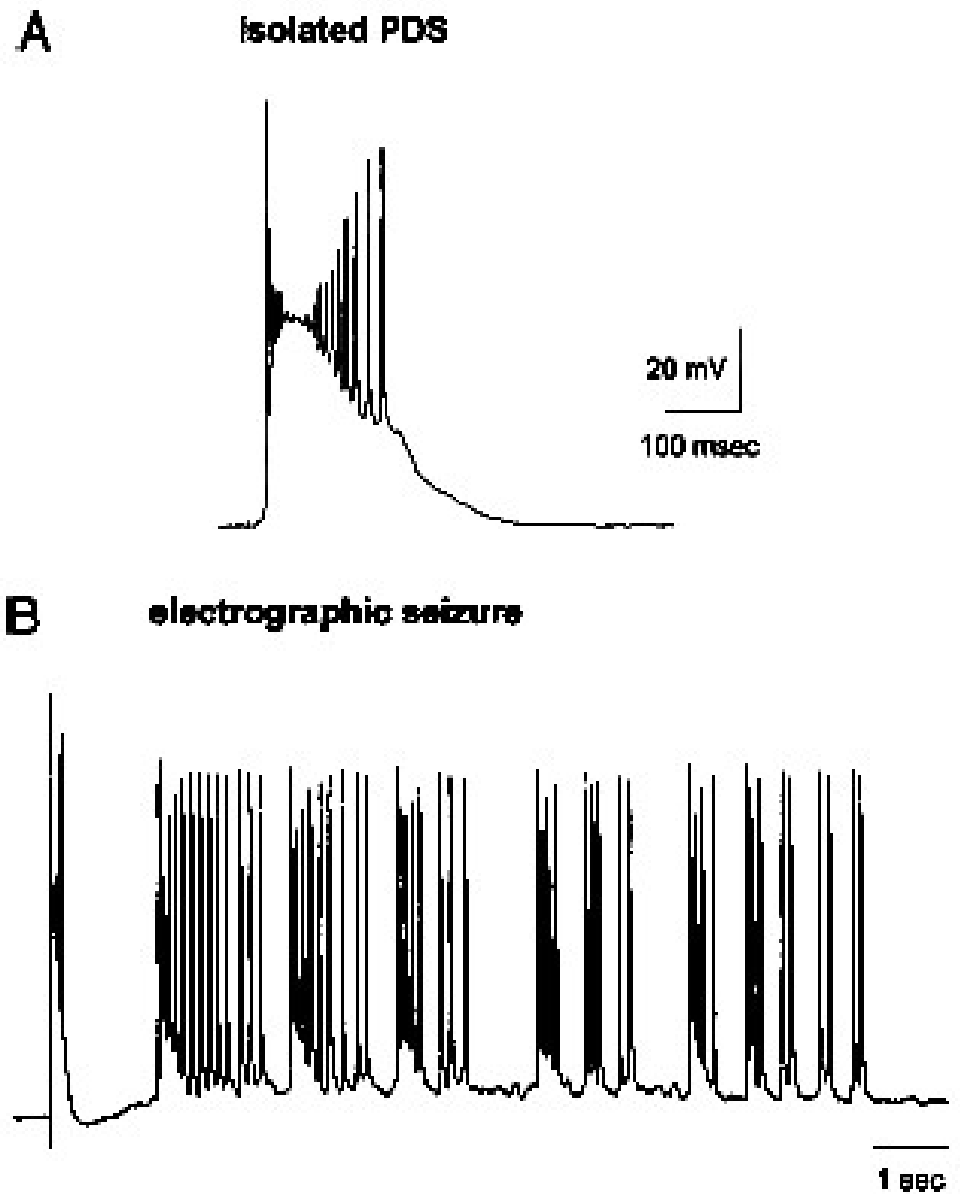
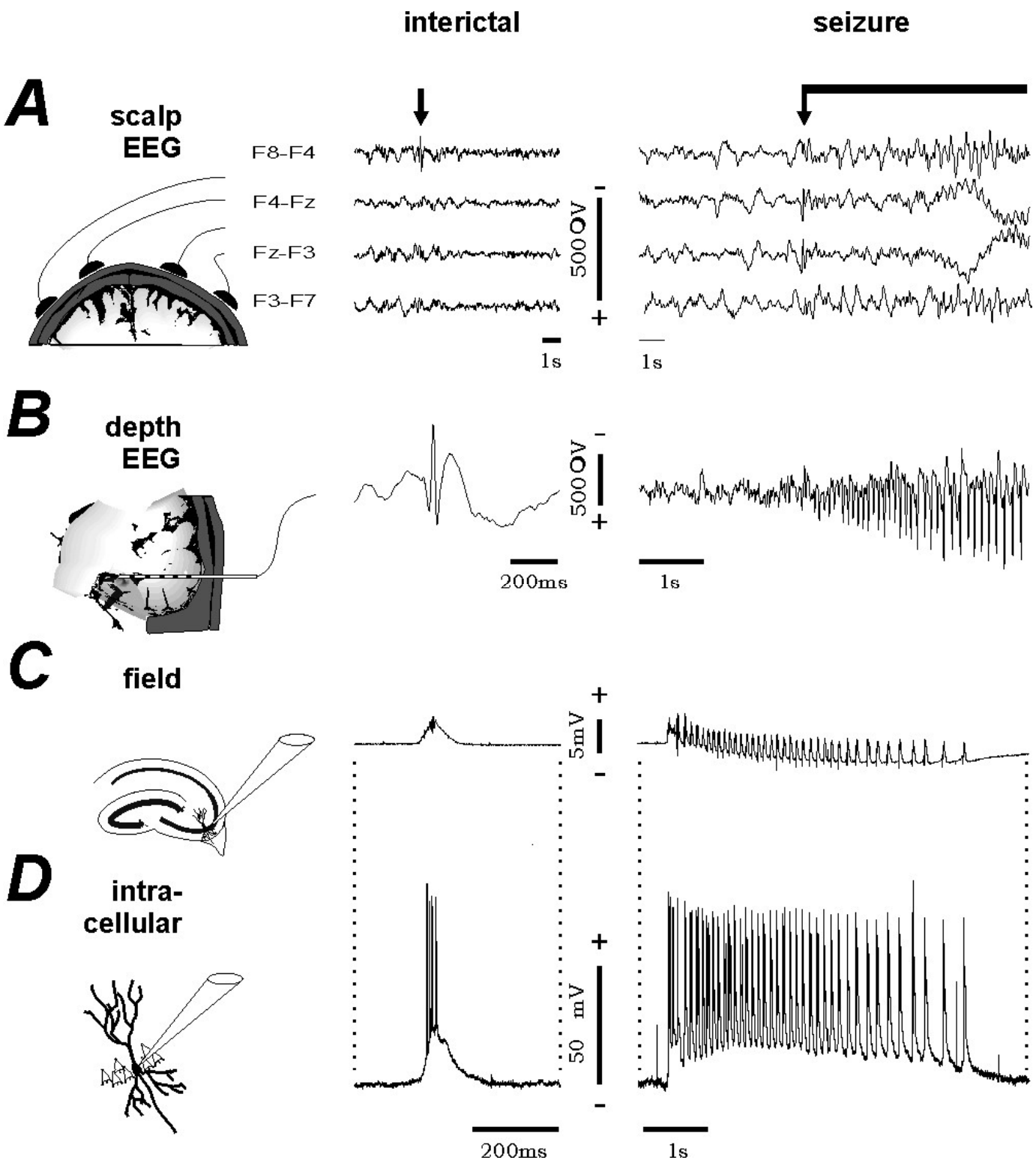


FIG. 1. Inter-ictal and ictal epileptic discharges. An isolated paroxysymal depolarization shift (PDS) response (*A*) and electrographic seizure (*B*) recorded with a somatic whole cell pipette from 2 different layer-5 pyramidal neurons. Both responses were evoked by extracellular synaptic stimulation in the presence 10 μM bicuculline (BCC) in the bath solution.


interictal
seizure
A
scalp
EEG
F8-F4
F4-Fz
Fz-F3
F3-F7
500 OV
1s
1s
B
depth
EEG
500 OV
200ms
1s
C
field
5mV
D
intra-
cellular
50 mV
200ms
1s

Animal models of epilepsy

PARTIAL

Simple partial, acute

Topical convulsants:

Penicillin
Bicuculline
Picrotoxin
Strychnine
Cholinergics

Acute electrical stimulation

Brain slices

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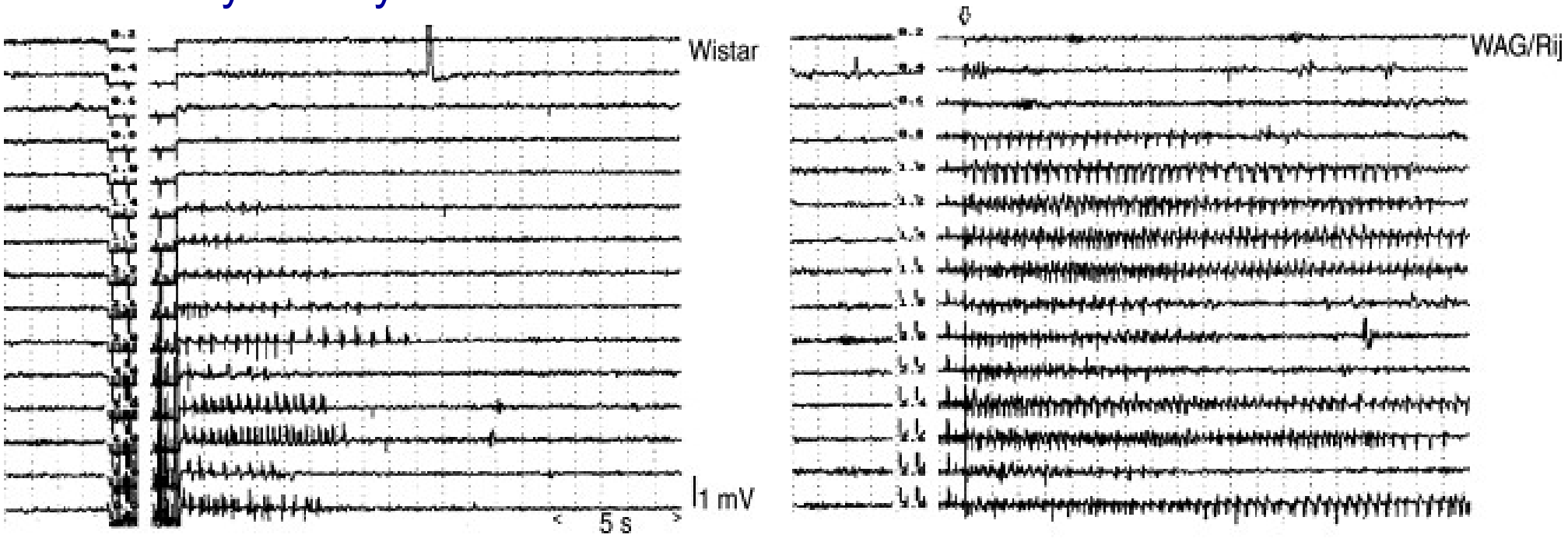
Systemic chemical convulsants:

Leptazol (pentylenetetrazol)
Picrotoxin
Bicuculline
Penicillin
Flurothyl

Models for focal seizures

Acute electrical stimulation

Repetitive direct electrical stimulation of cortical tissue *in vivo* using metal electrodes resting on the brain, can initiate EEG seizure afterdischarges recorded by nearby surface electrodes.



EEG recordings of effects of acute cortical stimulations of increasing intensity in control rats (0.2-3 mA) and WAG/Rij rats (0.2-10 mA) (3 month old rats).

Tolmachevea et al., 2004: Epilepsy Research 62, 189-198.

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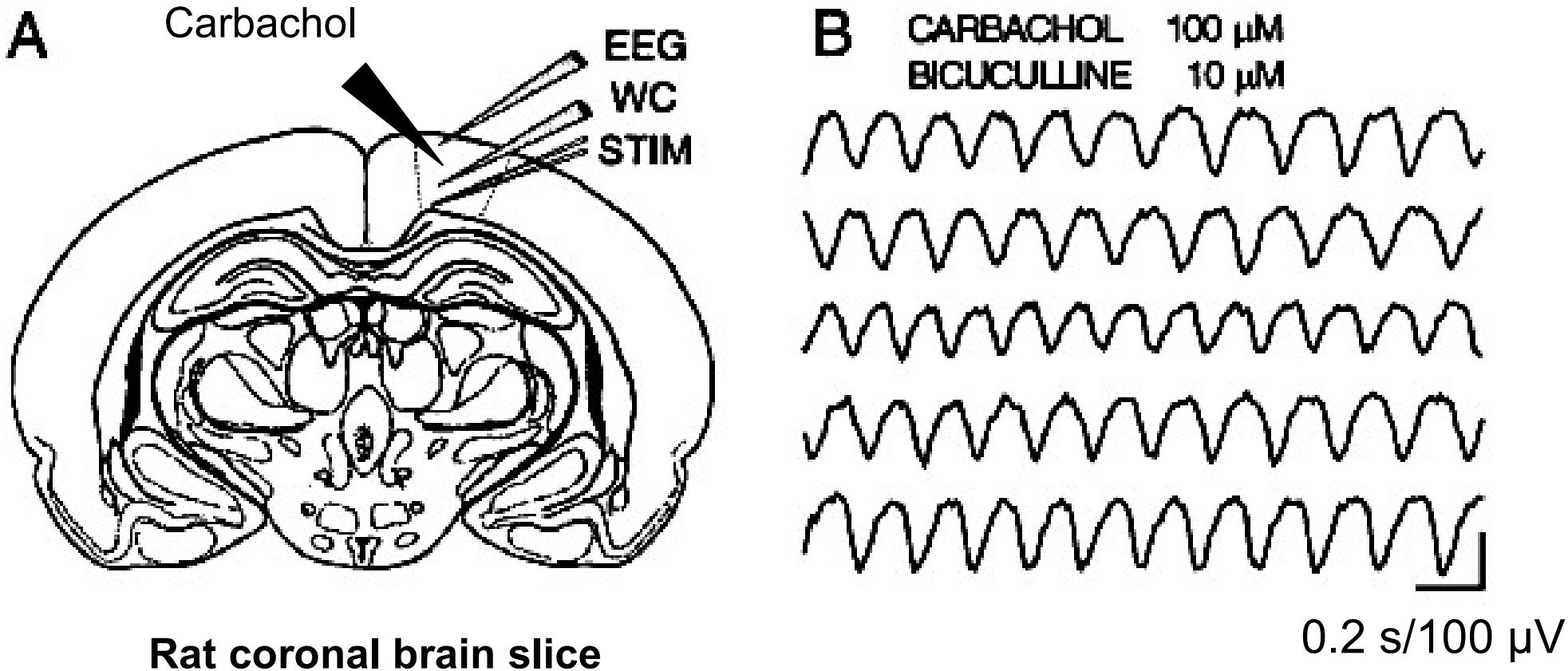
Bicuculline
Penicillin
Flurothyl

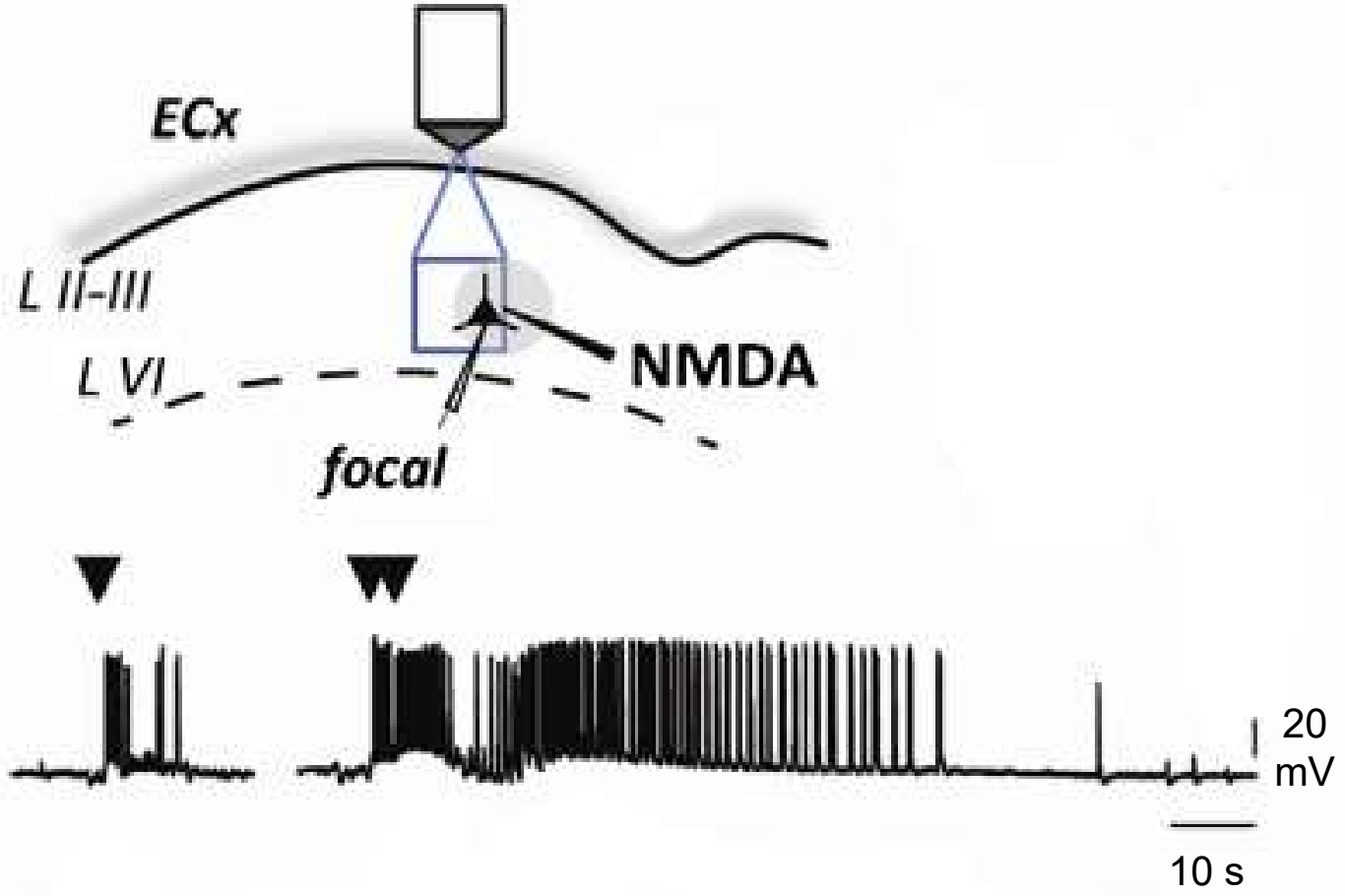
Neocortical brain slice preparation

Production of localized theta-frequency oscillations by focal application of carbachol



Rat coronal brain slice

Entorhinal cortex brain slice preparation



Focally-induced epileptiform burts in a rat entorhinal cortex slice preparation bathed in low Mg^{2+} + 100 µM 4AP. Brief pressure pulses of NMDA from a separate pipette are applied focally to the neurone recorded under whole cell patch. *From Losi et al., (2015) J. Neuroscience methods.*

Disadvantages of acute models

These methods tend to be rather **intense** - many cells in the focus participate in the epileptiform activity – this may not be the case in human foci.

Also, seizure discharges in such models generally last only minutes or hours – do not result in ***recurrent seizures*** – therefore, do not model the long-term time-dependent regional morphological changes in neurones/glia that may occur in human epileptic tissue.

Animal models of epilepsy

PARTIAL

Simple partial, chronic

Cortically implanted metals:

4% Aluminium hydroxide gel

Co, W, Zn, Fe

Complex partial

Kainic acid

Tetanus toxin

Kindling

Brain slices:

Rodent hippocampal/prepiriform cortical slices

Isolated cell preparations

Human neurosurgical tissue

GENERALIZED

Generalized absence

Thalamic stimulation

Bilateral cortical foci

Generalized penicillin (cat)

γ-OH butyrate (GHB)

Genetic rodent models

Status epilepticus

Lithium-pilocarpine

Cobalt focus epilepsy model

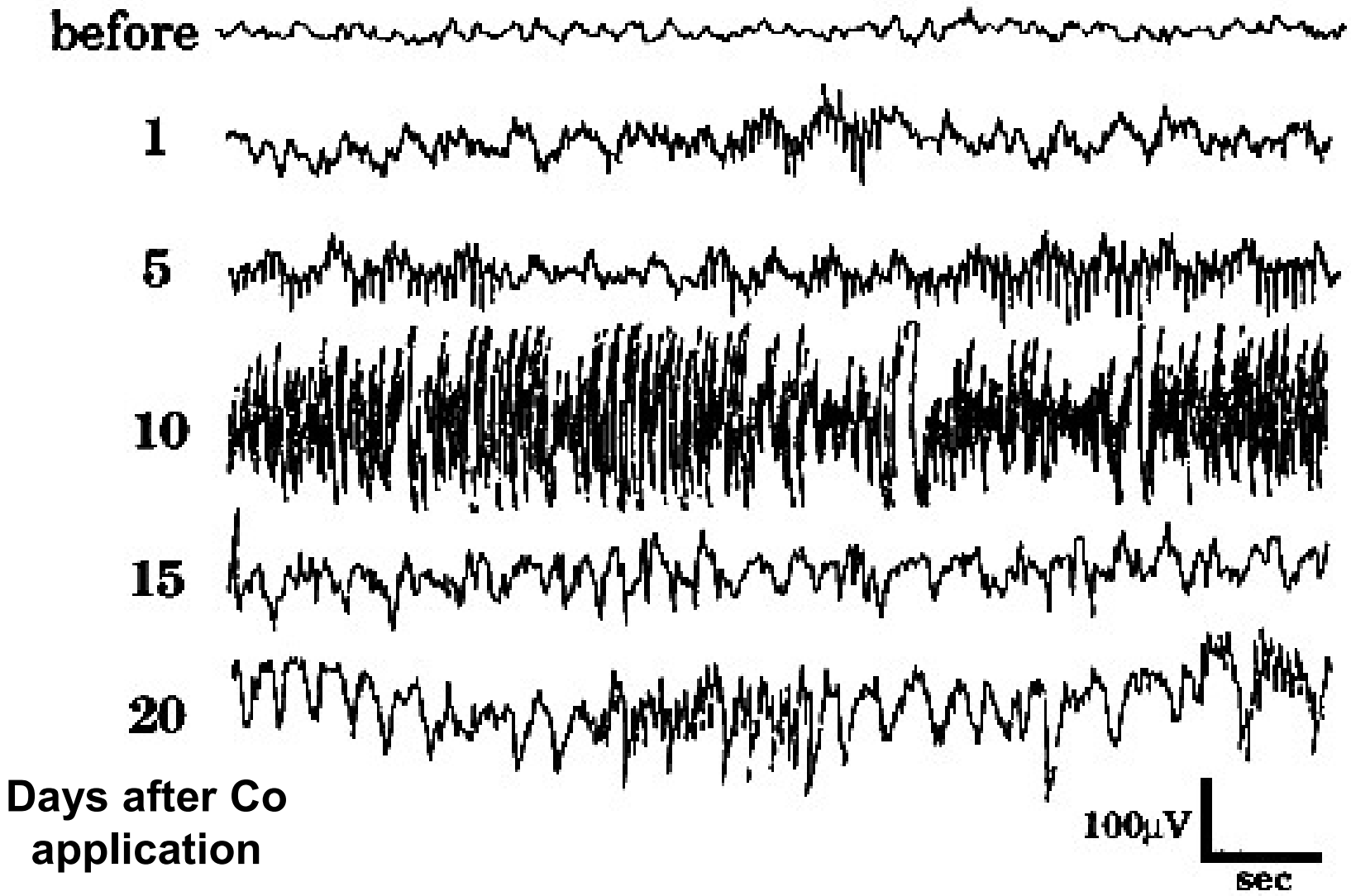


FIG. 2. EEG changes in the cobalt focus epilepsy model. Metallic cobalt powder (50 mg) was applied to the left cerebral cortex and the EEG was recorded on the right cerebral cortex. Before indicates at normal state and numbers on the left-hand side indicate days from cobalt application.

Animal models of epilepsy

PARTIAL

Simple partial, chronic

Cortically implanted metals:

4% Aluminium hydroxide gel

Co, W, Zn, Fe

Complex partial

Kainic acid

Tetanus toxin

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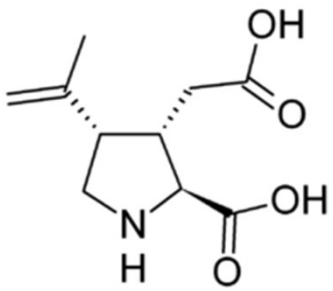
Lithium-pilocarpine

Kainic acid TLE model

This model presents with neuropathological and EEG features that are seen in patients with **temporal lobe epilepsy (TLE),** the most common form of complex partial epilepsy.

Kainic acid: is a potent rigid excitotoxic glutamate analogue (derived from a seaweed ***Digenea simplex*,** with prominent neurotoxic properties, particularly on hippocampal cells. In **sub-toxic** doses, kainic acid (applied *i.v.* or intra-hippocampally, where TLE often begins) can induce partial seizures in the hippocampus of animals by a disinhibitory mechanism. Such seizures can last hours or days, and may result in irreversible hippocampal lesions.

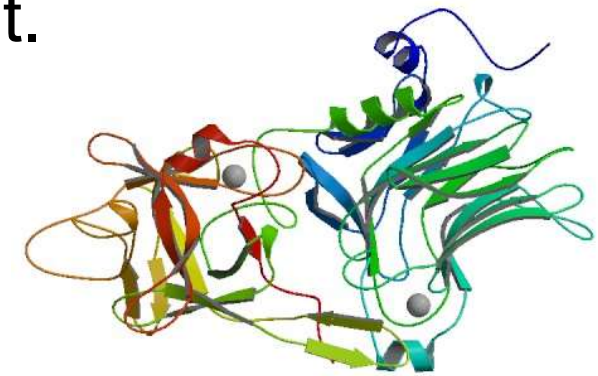


Kainic acid

Digenea simplex

Tetanus toxin TLE model

Tetanus toxin: low dose intra-cranial injections of tetanus toxin (derived from ***Clostridium tetani*** found in soil) into the rat hippocampus can induce recurrent chronic partial seizures over a period of weeks; thereafter, the incidence of seizures decreases until animals are seizure free. The exact mechanism of seizure induction is unclear, but may involve initially, a local interference with inhibitory **(GABA)** neurotransmitter release. Unlike the kainic acid model, hippocampal neuronal damage may or may not be present.



Tetanus toxin

Animal models of epilepsy

PARTIAL

Simple partial, chronic

Cortically implanted metals:

4% Aluminium hydroxide gel

Co, W, Zn, Fe

Complex partial

Kainic acid

Tetanus toxin

Kindling (consistent with human partial epilepsy)

Brain slices:

Rodent hippocampal/olfactory cortical slices

Isolated cell preparations

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GENERALIZED

Generalized absence

Thalamic stimulation

Bilateral cortical foci

Generalized penicillin (cat)

γ-OH butyrate (GHB)

Genetic rodent models

Status epilepticus

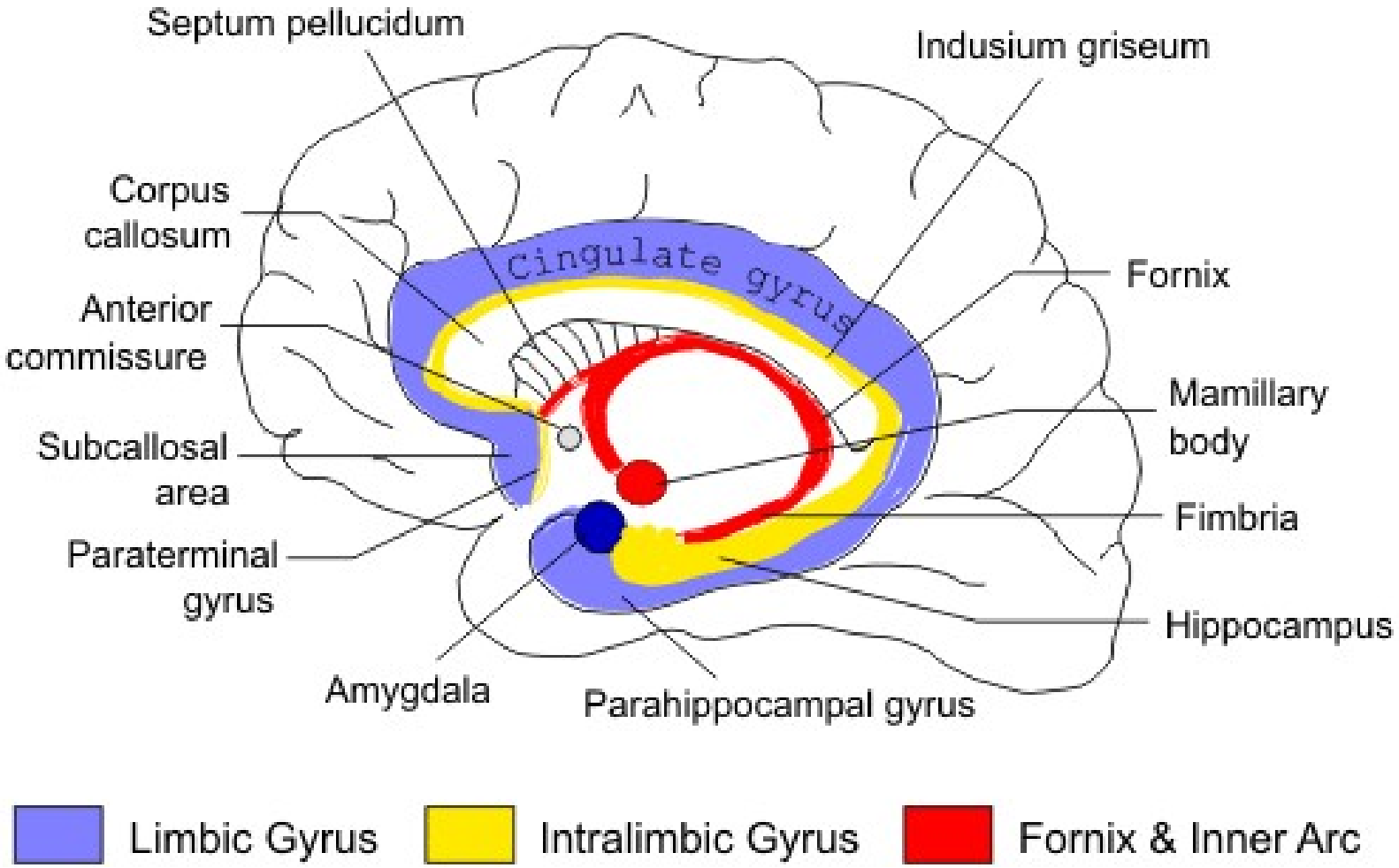
Lithium-pilocarpine

Limbic kindling

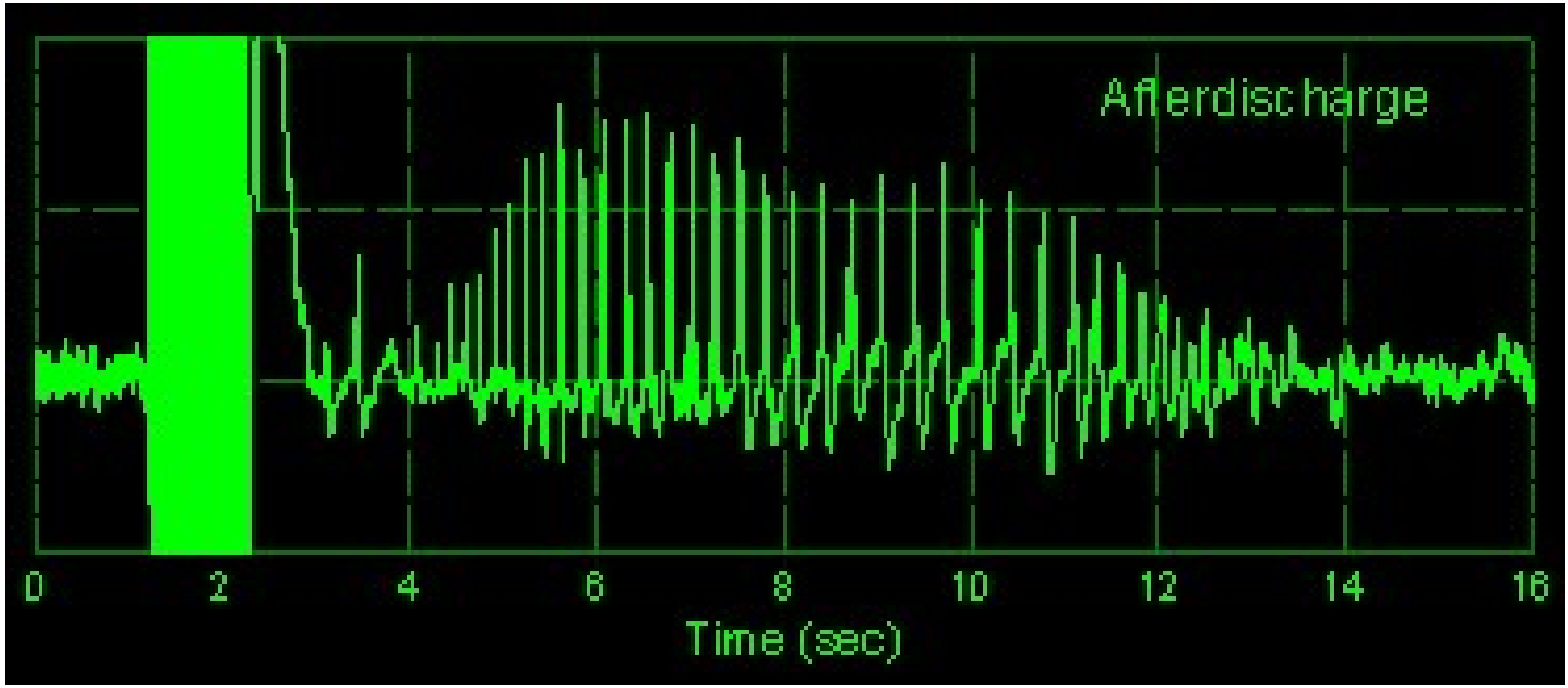
Kindling: repeated sub-convulsive electrical shocks applied to various parts of the brain *(e.g*. the amygdala), delivered over a period of days via implanted electrodes, eventually causes a lasting change in brain excitability, so that after a few weeks, 'kindled' animals exhibit permanent spontaneous partial and generalized seizures. The kindling model is a good model of secondarily generalized complex partial seizures.

Repeated small doses of **leptazol** can also cause permanent 'chemical kindling'-long-lasting 'plastic' changes in synaptic connectivity, and altered function of excitatory and inhibitory amino acid receptors in individual neurones occurring. Phenobarbitone, diazepam phenytoin and carbamazepine block seizure *occurrence.*

The Limbic System



Basic properties of experimental kindling



EEG afterdischarge in a kindled rat, generated in the CA3-CA1 part of the "trisynaptic circuit" of the hippocampus, which with the amygdala and several other cortical regions make up the limbic system. A second and a half of normal hippocampal EEG precedes the 1 sec 60Hz kindling train, which is followed by a brief flattening of the EEG, and then by a growing, 3Hz synchronous bursting.

Amygdala-kindled rat

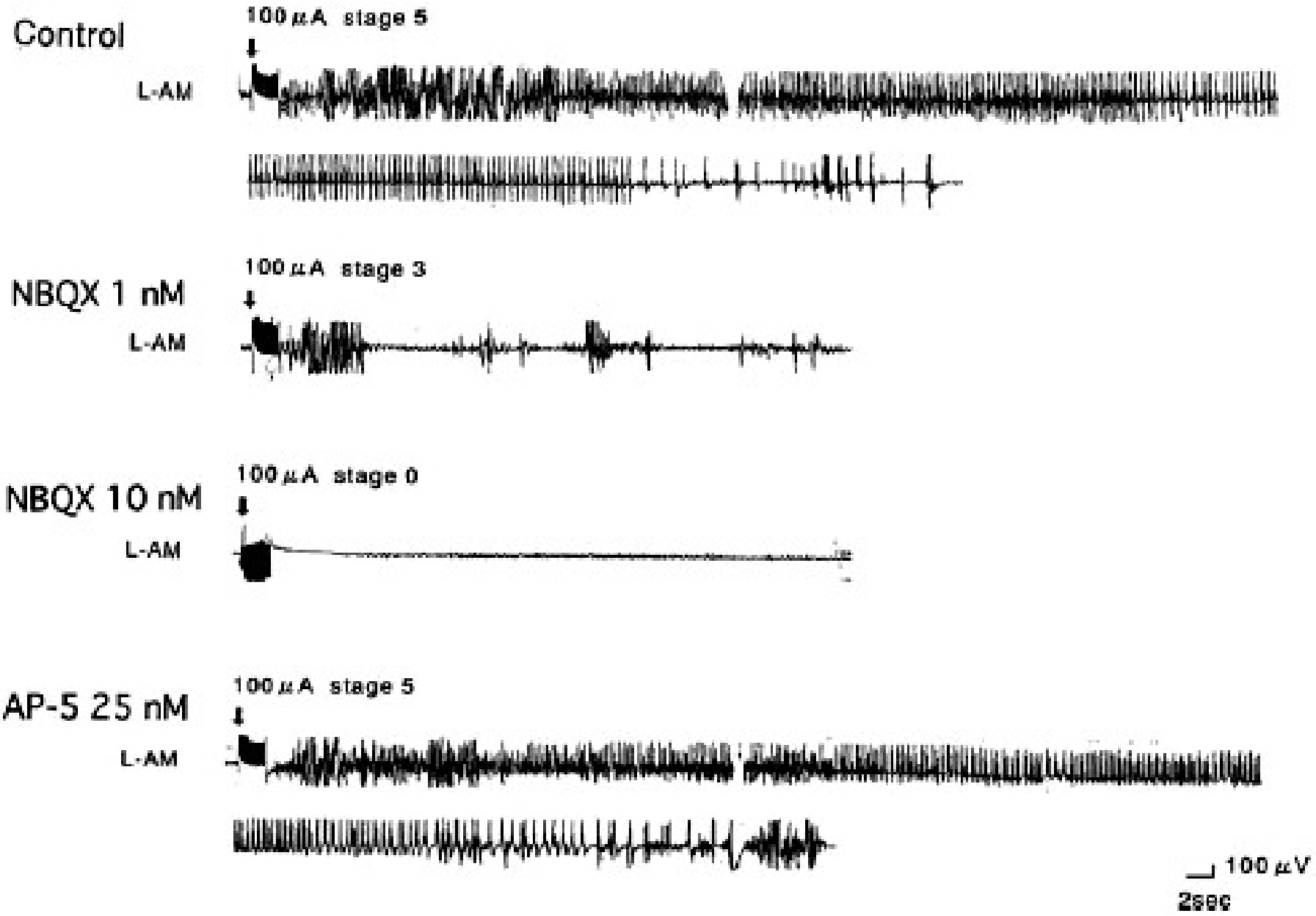


Fig. 4. The anticonvulsant effects of direct microinjection of a selective antagonist of AMPA receptors (NBQX-Na) and NMDA receptors (AP-5) into the kindled amygdala in amygdala kindled rats. NBQX (1 and 10 nM) suppressed afterdischarges recorded from the stimulated left-amygdala (L-AM), in a dose-dependent manner, while AP-5 (25 nM) had no effects. Data are from Morimoto and Hirao (unpublished data).

Animal models of epilepsy

PARTIAL

Simple partial, chronic

Cortically implanted metals:

4% Aluminium hydroxide gel

Co, W, Zn, Fe

Complex partial

Kainic acid

Tetanus toxin

Kindling

Brain slices:

Rodent hippocampal/olfactory cortical slices

Isolated cell preparations

Human neurosurgical tissue

GENERALIZED

Generalized absence

Thalamic stimulation

Bilateral cortical foci

Generalized penicillin (cat)

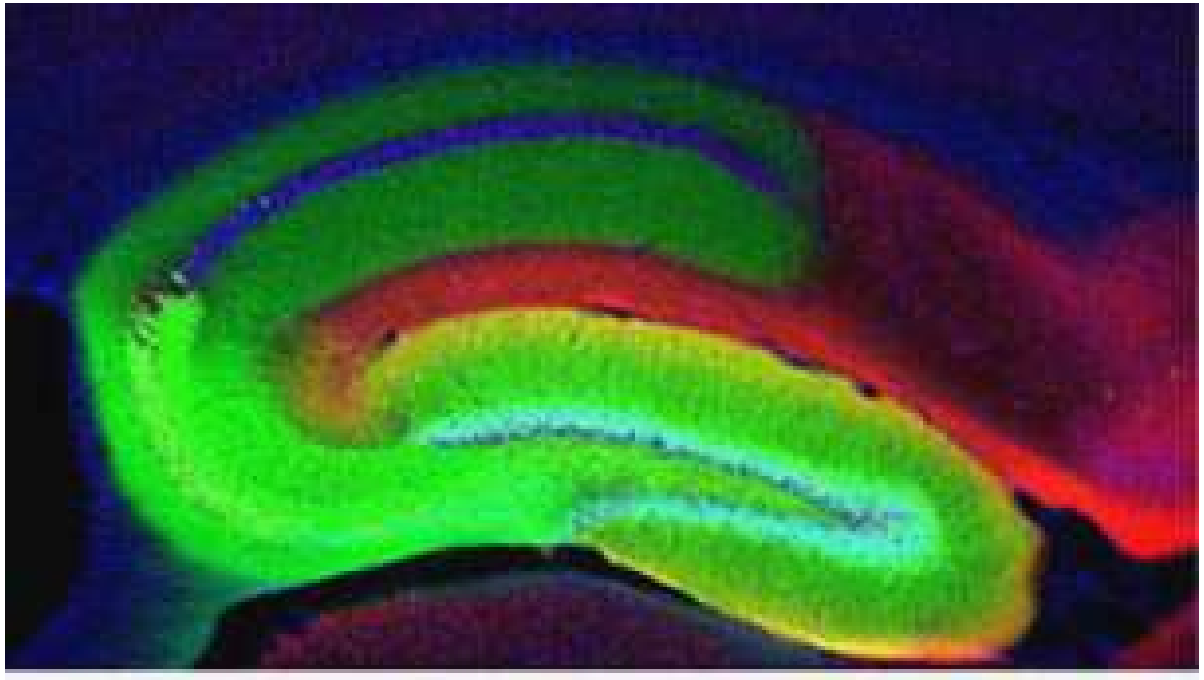
γ-OH butyrate (GHB)

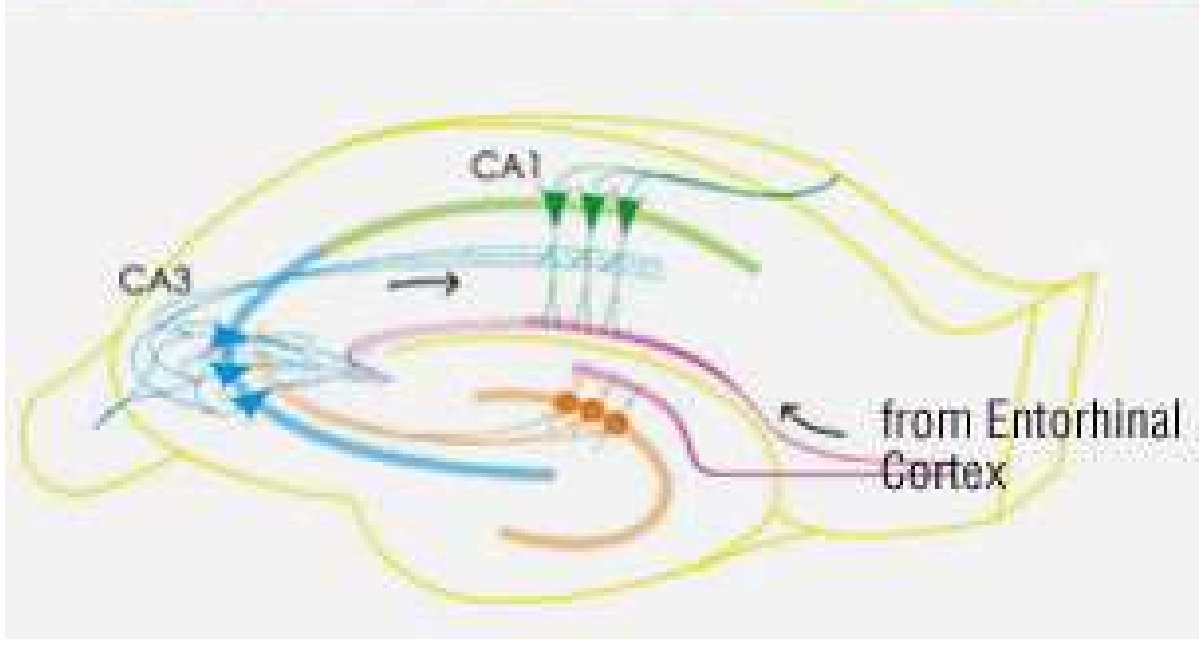
Genetic rodent models

Status epilepticus

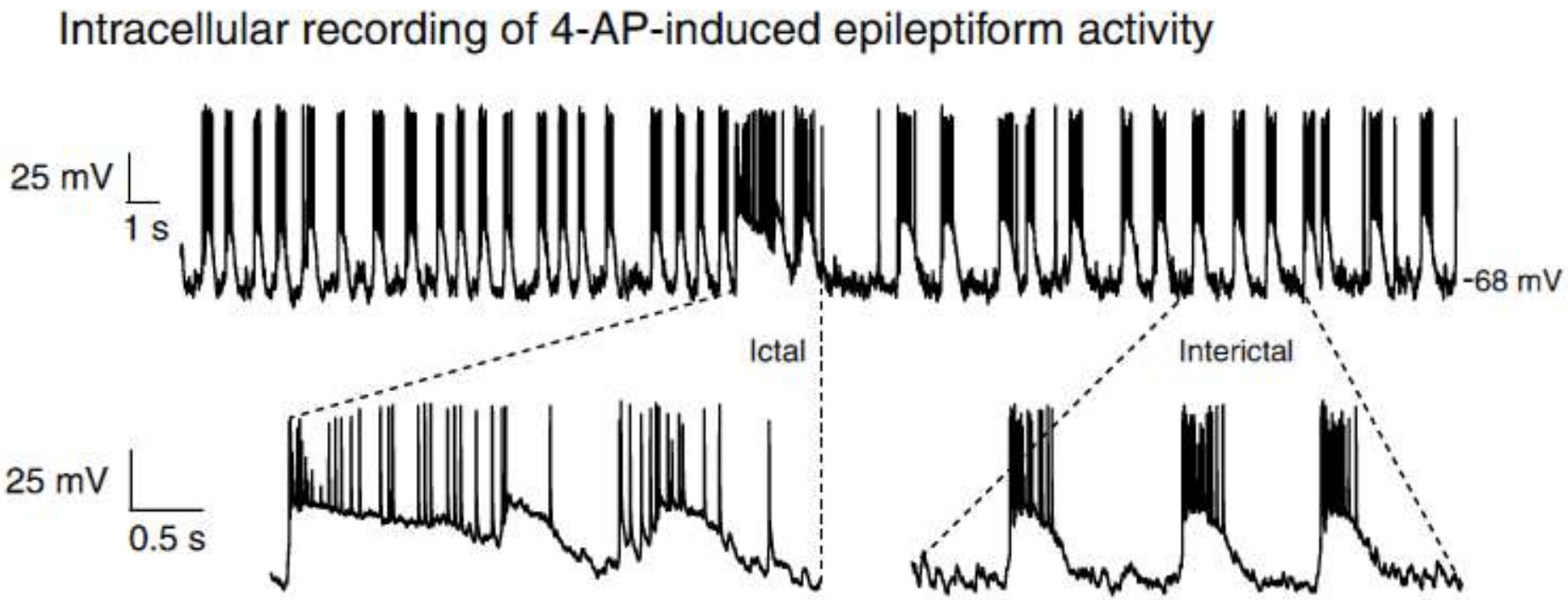
Lithium-pilocarpine

Hippocampal brain slice model



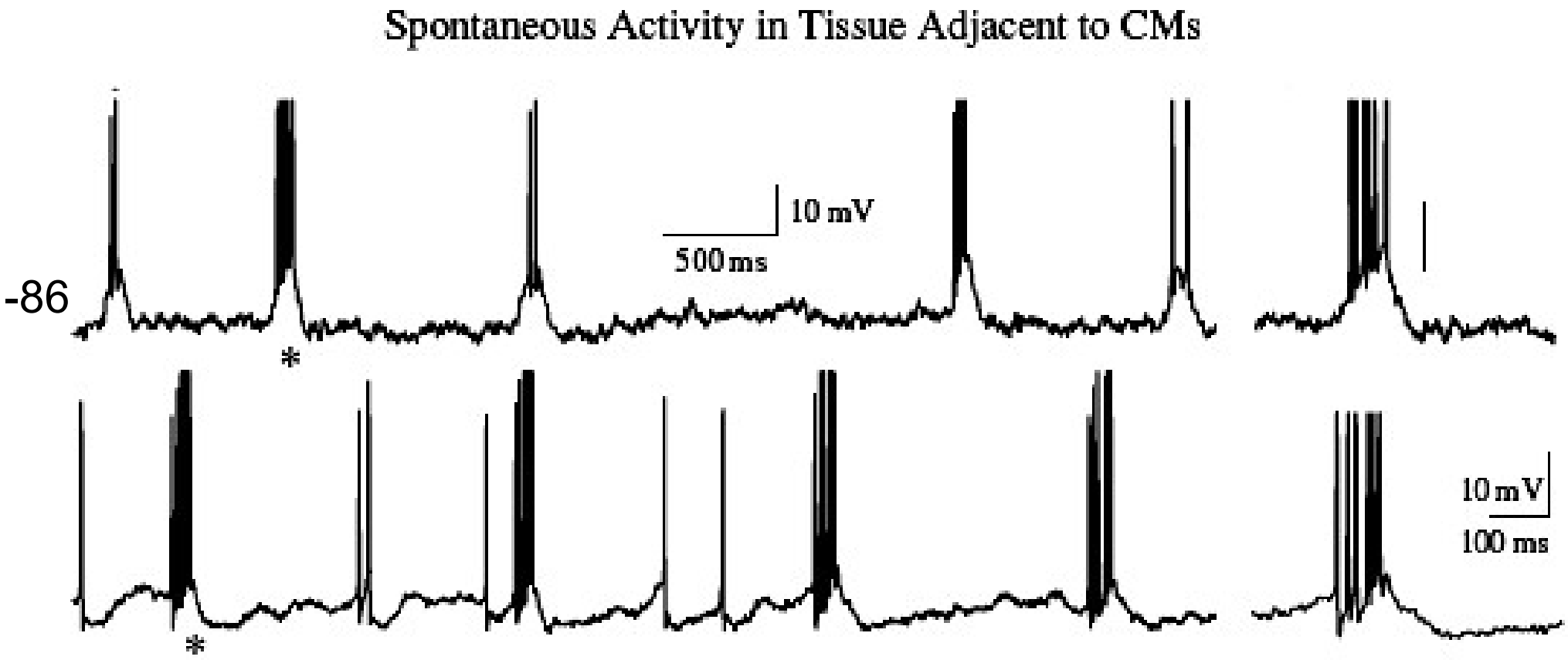


Hippocampal brain slice preparation



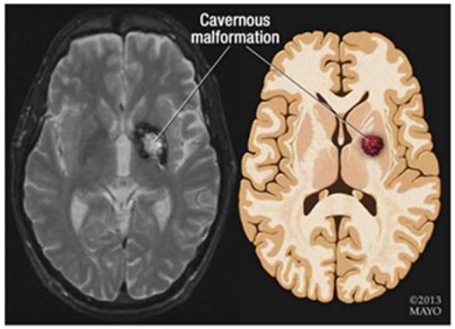
4-AP (100 μM)-induced epileptiform activity recorded intracellularly from a CA1 hippocampal brain slice neurone. The epileptiform activity included distinct ictal and interictal epochs. (D) S. Toprani, D.M. Durand; Experimental Neurology 240 (2013) 28–43

Human neocortical brain slice preparation

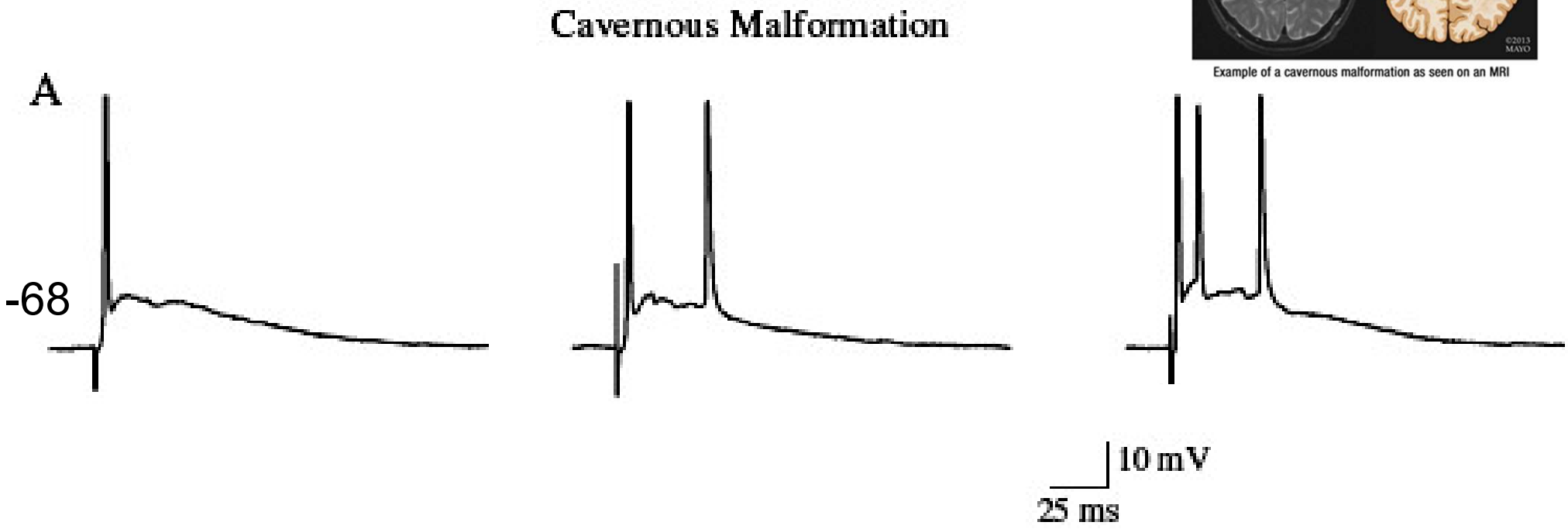


Example of spontaneous activity recorded intracellularly in human neocortical cell adjacent to a cavernous malformation.

Human neocortical brain slice preparation



Example of a cavernous malformation as seen on an MRI

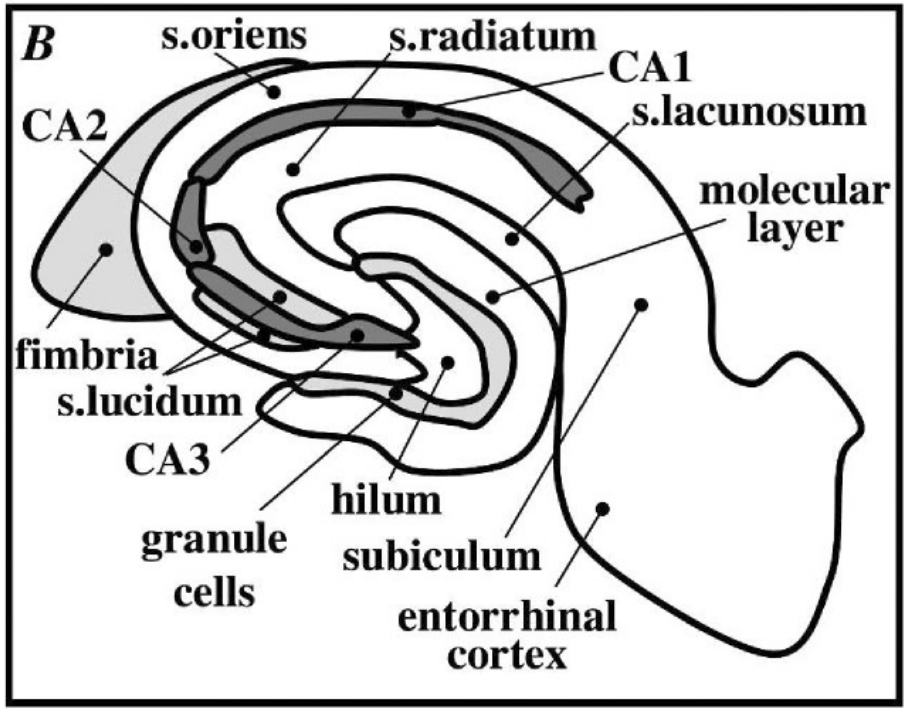


Example of synaptically-evoked epileptiform responses recorded intracellularly in human neocortical cell adjacent to a cavernous malformation


Take a
Break!

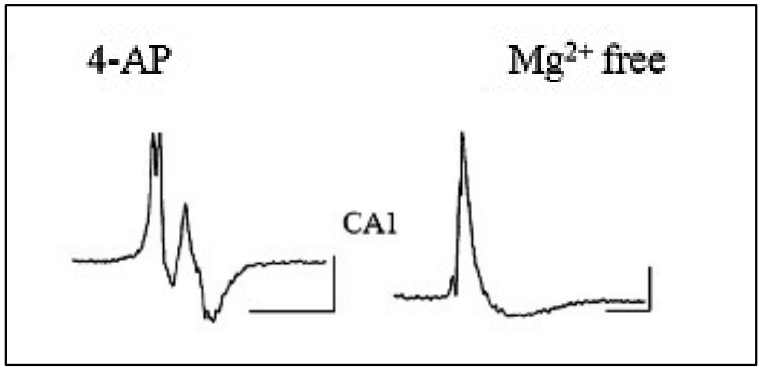
Hippocampal brain slice model

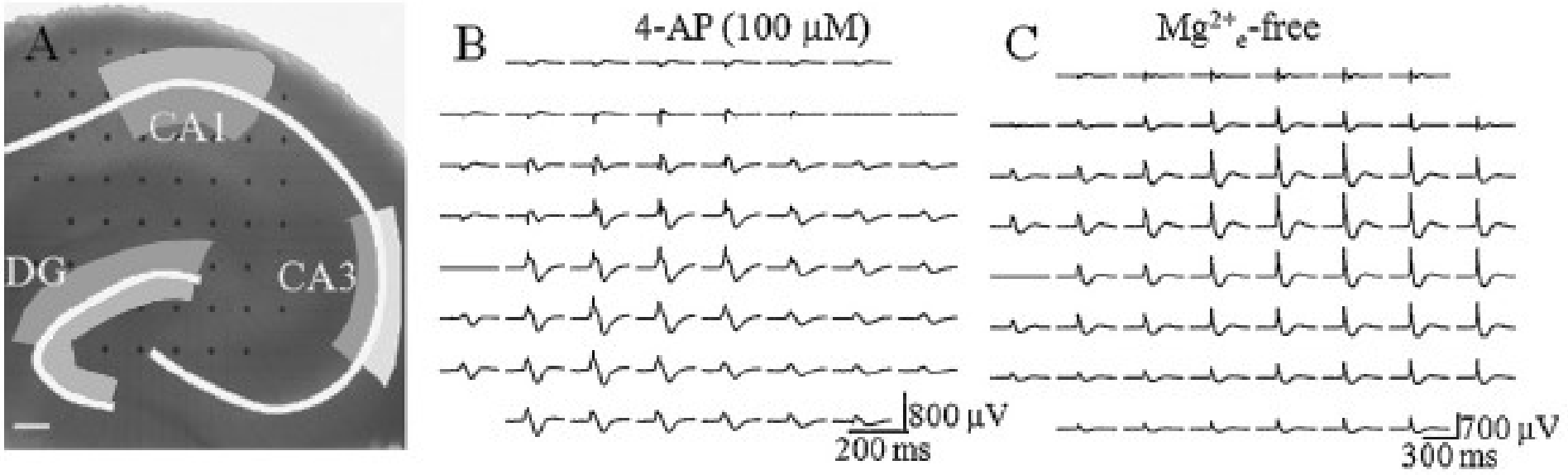
Multi-electrode array (MEA) recording



Hippocampal brain slice model

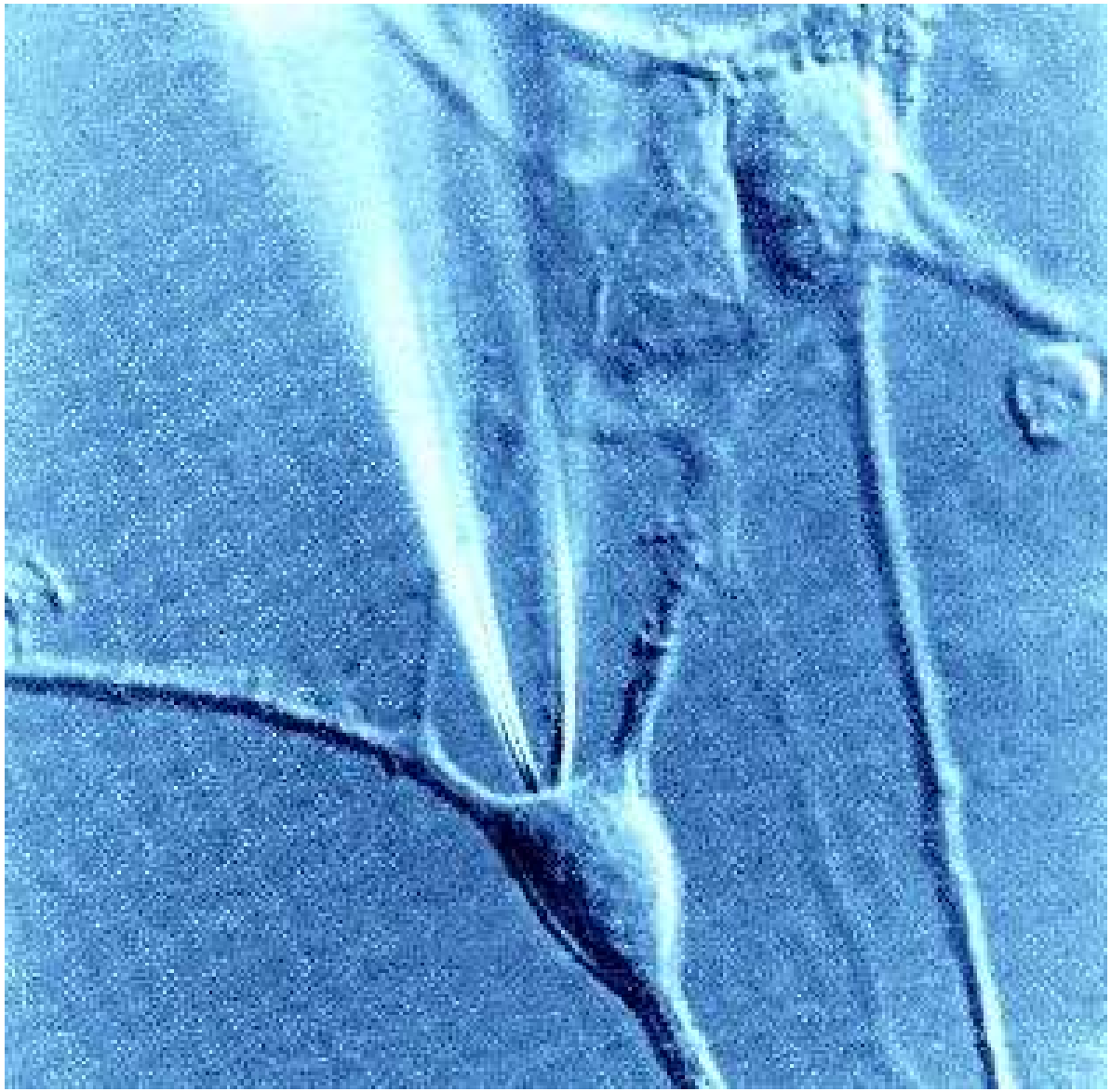
Multi-electrode array (MEA) recording



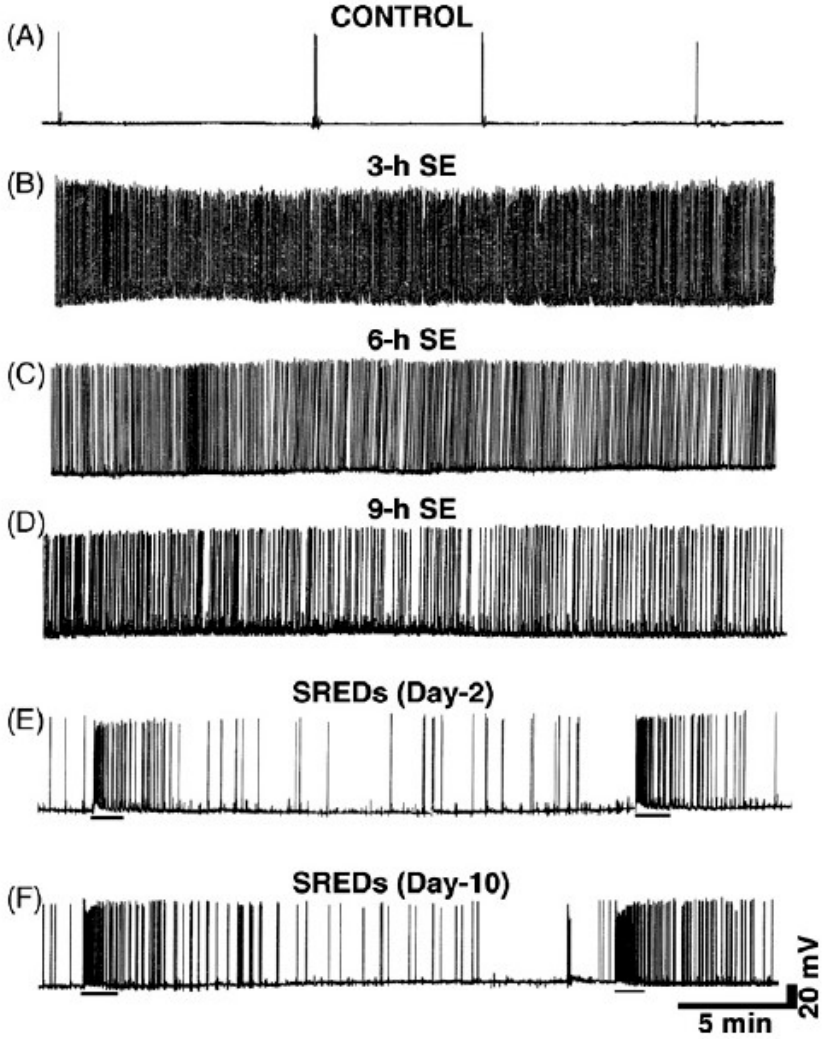


Epileptiform burst characteristics in hippocampal slices recorded on an MEA. (A) Image of hippocampal slice from adult rat (P30) mounted on an MEA (scale bar: 200 µm). (B,C) Epilleptiform bursts across the entire MEA induced by 100 µM 4-AP (B) or Mg^{2+} -free aCSF (C). Inset shows single field potentials: (Scale bars:100 µV; 100 ms.

A patch pipette on a cultured neurone



Cultured neurone preparation



Continuous high-frequency epileptiform discharges (SE) and spontaneous recurrent epileptiform discharges (SREDs) recorded under whole-cell patch clamp in cultured hippocampal neurones (14 DIC). (A) Control neurone showing occasional spontaneous action potentials. (B-D) Neurone during low-Mg^{2+} exposure (3, 6 and 9 h) showing induction of tonic high-frequency epileptiform bursts. (E-F) Neurones 2 and 10 days after low Mg^{2+} exposure (3 h). SREDs persist for the life of the neurones in this culture model.

Animal models of epilepsy

PARTIAL

Simple partial, acute

Topical convulsants:

Penicillin
Bicuculline
Picrotoxin
Strychnine
Cholinergics

Acute electrical stimulation

Neocortical brain slices

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Flurothyl

Audiogenic seizures in mice

DBA/2 are an inbred strain of mice that are susceptible to sound-induced generalized seizures, typically between the age of 2-4 weeks; by the 8th week, their susceptibility declines. When the mice are exposed to a loud sound at 12-16 kHz (90-120 dB; 1 min), they display a characteristic seizure pattern consisting of a wild running phase, clonic jerks, tonic extension followed by respiratory arrest or full recovery. Although there is no direct human counterpart, the model has become a commonly used general method of inducing gross generalized seizures for the purpose of screening new AEDs.

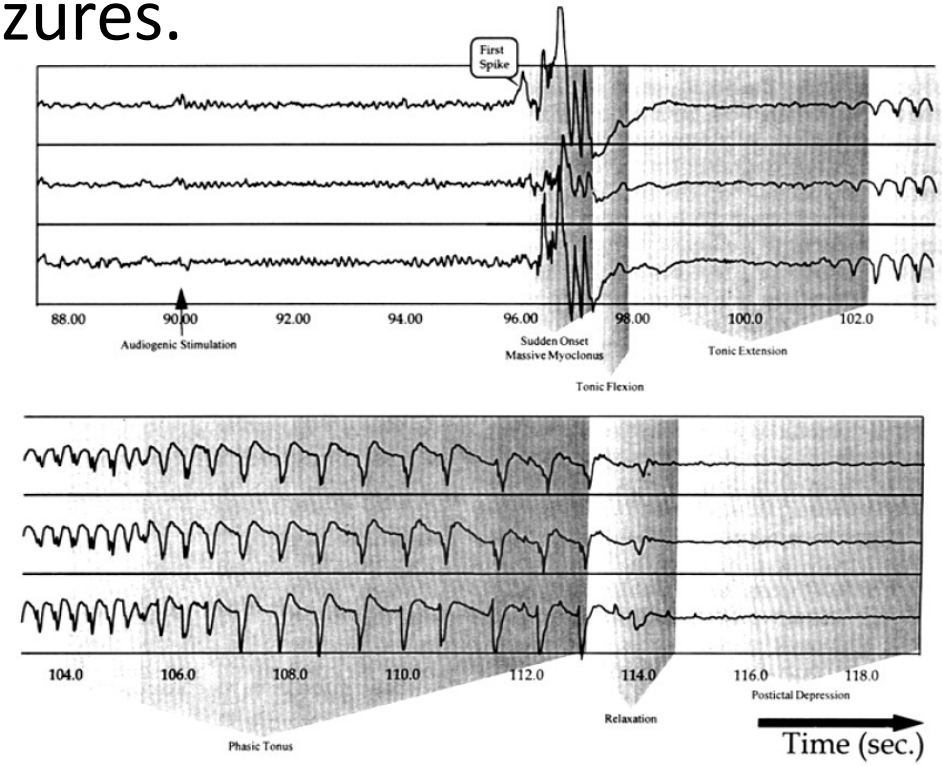
Genetic animal models of epilepsy

Totterer are a homozygous strain of mice that are genetically prone to frequent spontaneous epileptic seizures from the age of 3-4 weeks. They also express a broad ataxic gait. In addition to generalized seizures they also exhibit absence-type seizures, hence the two seizure types can be studied in one model.

EL mice are a standard genetic model of sensory-precipitated generalized epilepsy; they also show behavioural abnormalities similar to ***human autism*** (impairment in social interaction/communication) [~30% of individuals with autism develop epilepsy by adulthood]. EL mice could therefore be used as a natural model of autism and co-morbid epilepsy.

Genetically Epilepsy-Prone Rats

GEPRs are genetically epilepsy-prone rats in which generalized seizures can be readily induced by various stimuli *e.g.* electrical, chemical, sound or hyperthermia. The seizure pattern consists of a wild running phase, clonic jerks, tonic extension, followed by respiratory arrest or full recovery. They are a good model for testing new AEDs *vs*. tonic-clonic seizures.



Animal models of epilepsy

PARTIAL

Simple partial, acute

Topical convulsants:

Penicillin
Bicuculline
Picrotoxin
Strychnine
Cholinergics

Acute electrical stimulation

Neocortical brain slices

GENERALIZED

Generalized tonic-clonic

Genetic:

Audiogenic seizures in mice
"Totterer" and *"EL" mice*
Genetically epilepsy-prone rats

Maximal electroshock (MES)

Systemic chemical convulsants:

Leptazol (pentylenetetrazol)
Picrotoxin
Bicuculline
Penicillin
Flurothyl

Maximal electroshock model (MES)

This is commonly used method of inducing acute generalized seizures in mice or rats for testing new compounds that may be effective against generalized tonic-clonic seizures. Electrical stimuli of varying intensity (50 mA mouse, 150 mA rat: 0.2s) are applied via ear-clips (or corneal electrodes) to evoke tonic hind limb extensions that can be suppressed by AEDs. The ED_{50} for suppression of tonic hind limb extension is calculated as a measure of AED potency. **Not all AEDs are effective in this test.**

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Systemic chemical convulsants

Numerous compounds can produce generalized tonic-clonic seizures when administered systemically *e.g.* **leptazol, penicillin, picrotoxin and bicuculline.** All induce seizures by interfering with $GABA_A$-mediated synaptic inhibition. The action of leptazol may also involve other mechanisms.

In the **flurothyl model of neonatal seizures,** the inhalant anaesthetic **flurothyl** is administered to rat pups during P7-10, to produce multiple recurrent generalized seizures, most likely by blocking $GABA_A$ synaptic transmission. Testing new AEDs against MES and leptazol-induced seizures, is now a routine screening test. Note: phenytoin is effective *vs.* MES, but <u>not</u> *vs*. leptazol seizures.

Animal models of epilepsy

PARTIAL

Simple partial, chronic

Cortically implanted metals:

4% Aluminium hydroxide gel

Co, W, Zn, Fe

Complex partial

Kainic acid

Tetanus toxin

Kindling

Brain slices:

Rodent hippocampal/prepiriform cortical slices

Isolated cell preparations

Human neurosurgical tissue

GENERALIZED

Generalized absence

Thalamic stimulation

Bilateral cortical foci

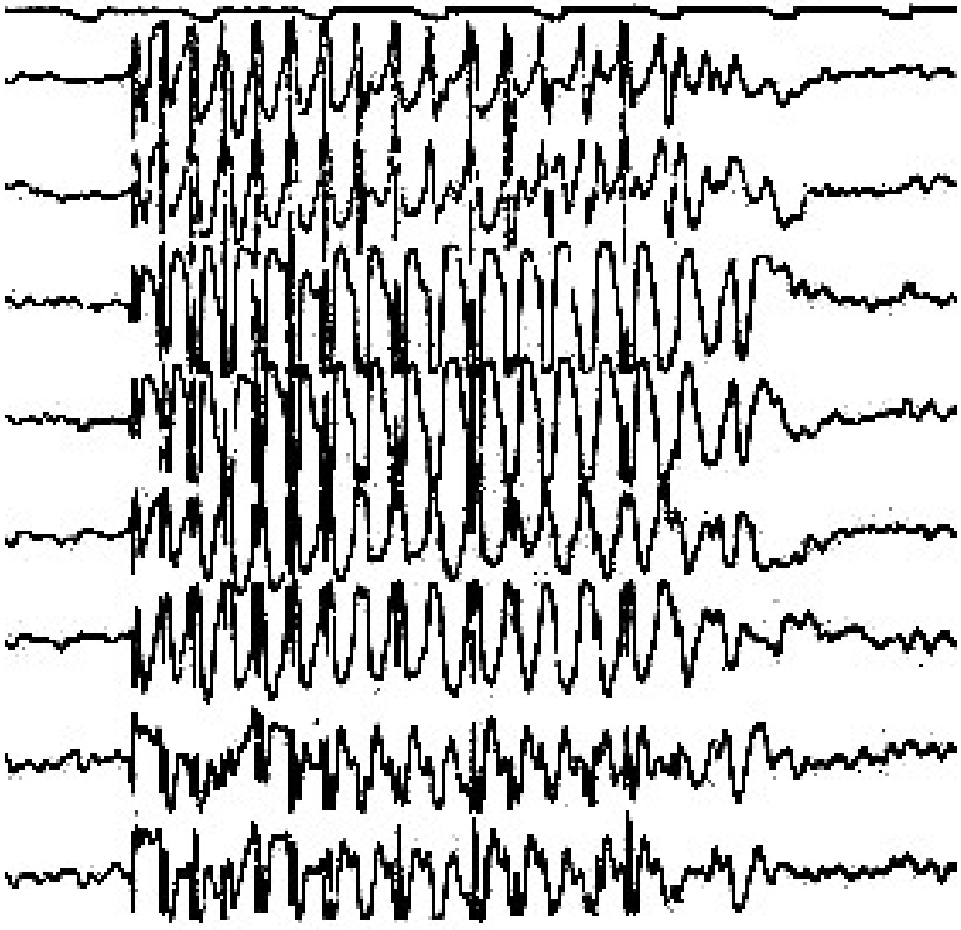
Generalized penicillin (cat)

γ-OH butyrate (GHB)

Genetic rodent models

Status epilepticus

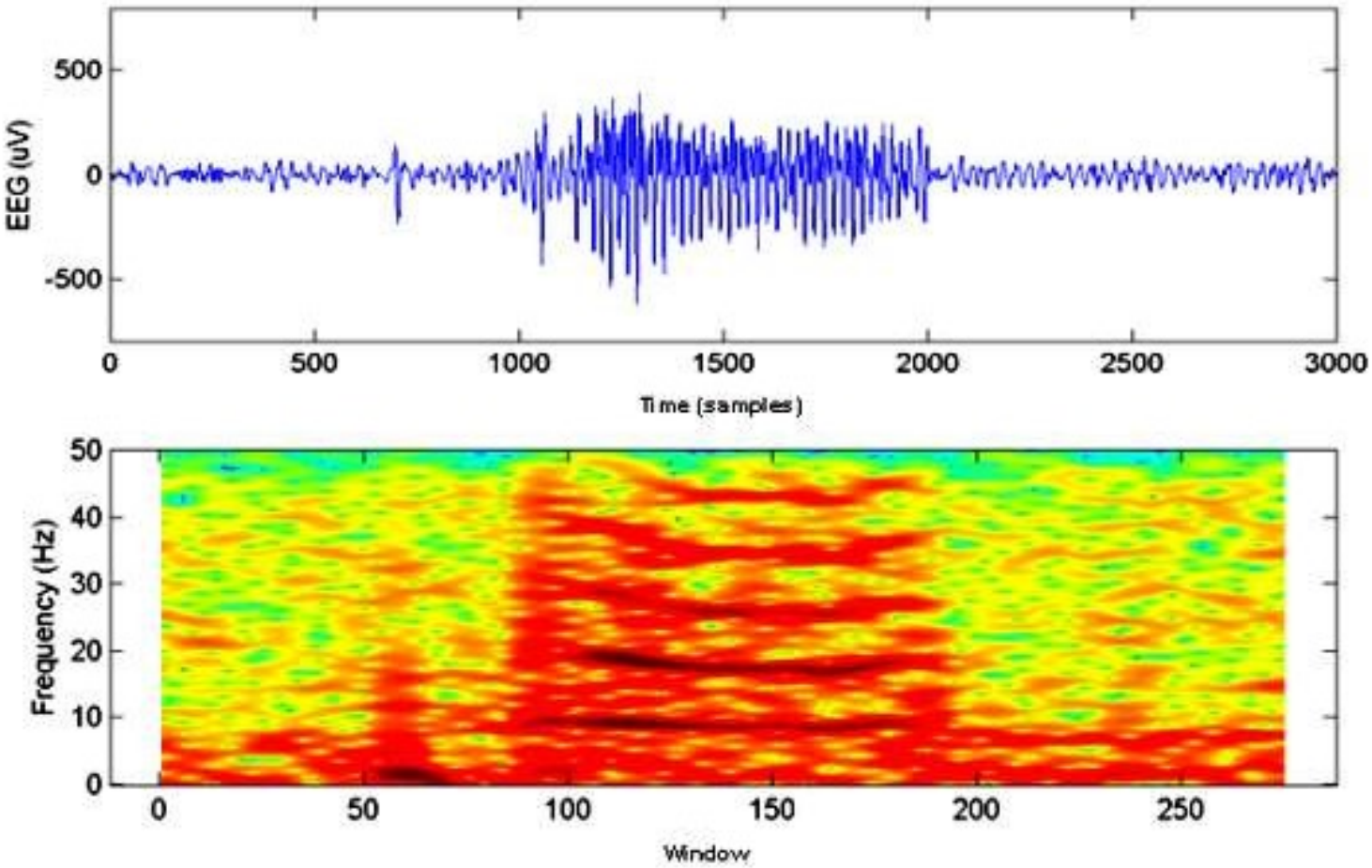
Lithium-pilocarpine



EEG during an absence seizure

Long outbreak of generalized spike-and-slow wave discharges (1.5-2.5 Hz) recorded in a human patient. During this period, the patient stares at a point and does not react. This is a typical absence seizure.

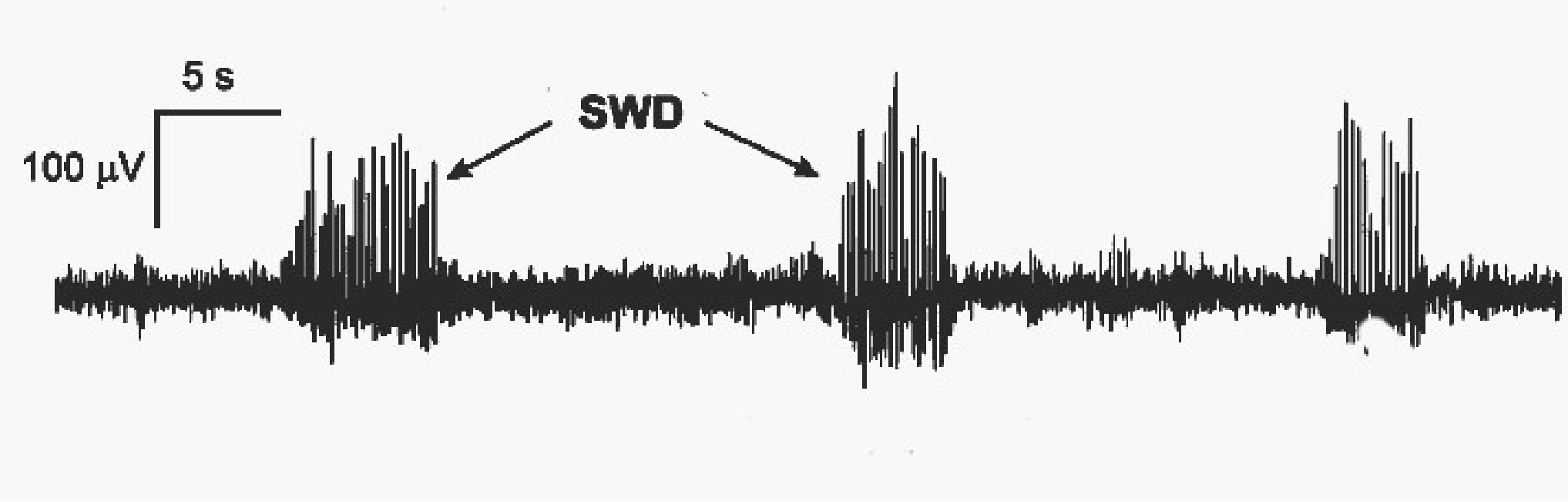
GAERS (Genetic Absence Epilepsy Rats from Strasbourg)



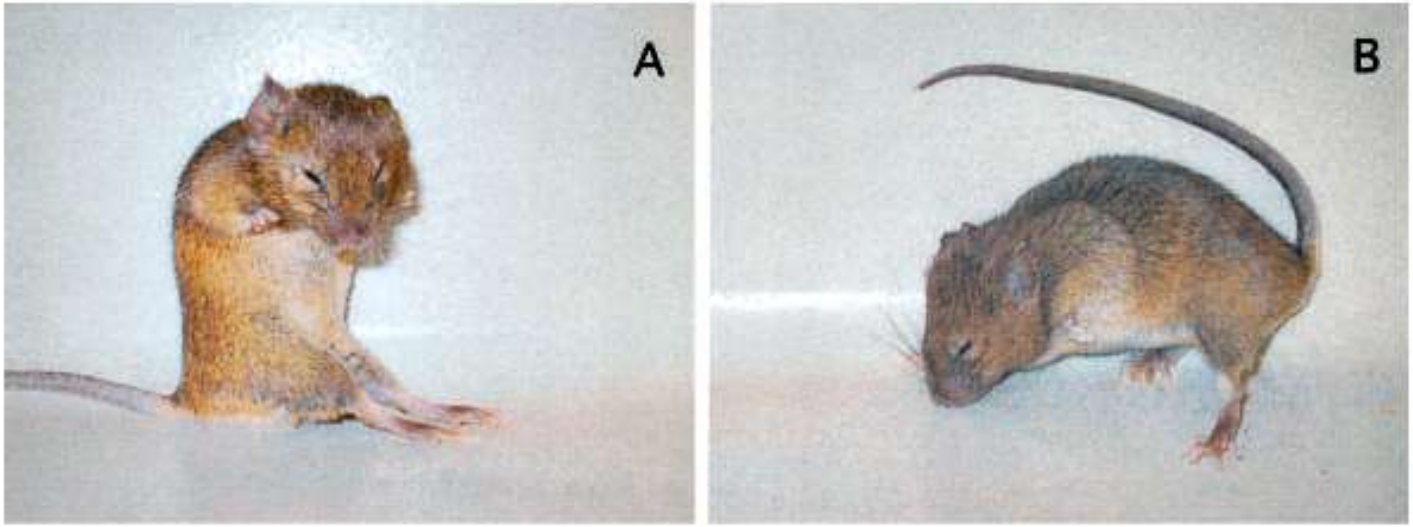
SWD in cortical EEG of GAERS

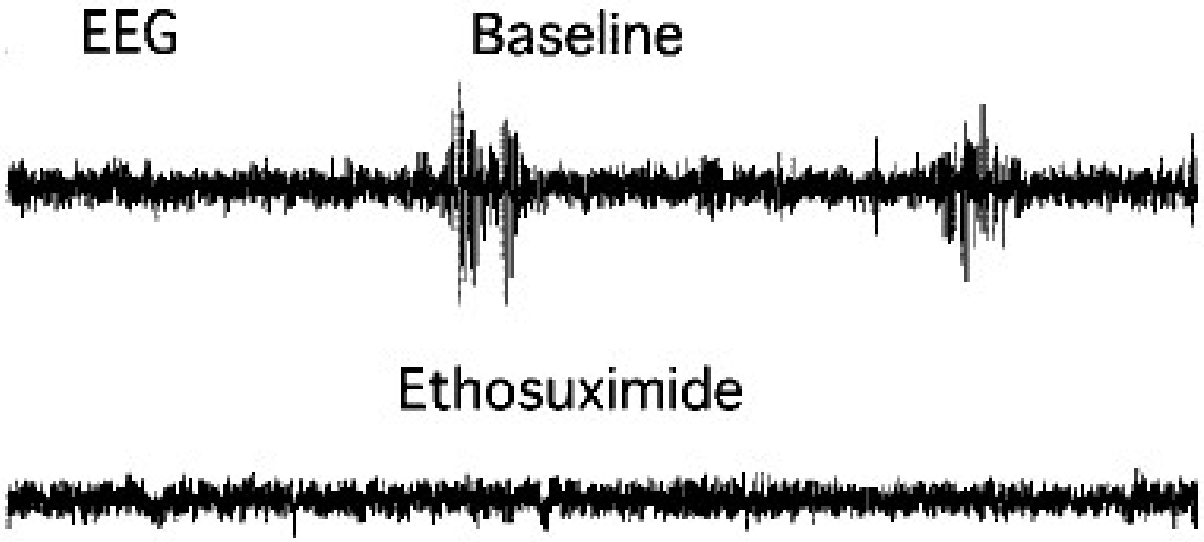
GAERS (Genetic Absence Epilepsy Rats from Strasbourg) are a strain of Wistar rats that exhibit generalized non-convulsive epileptic seizures similar to those observed in human absence epilepsy. During these episodes, the cortical EEG displays bilateral and synchronous SWD (Spike and Wave Discharges) all over the cortex.

WAG/Rij rat model of absence epilepsy



Lethargic mouse model of absence epilepsy





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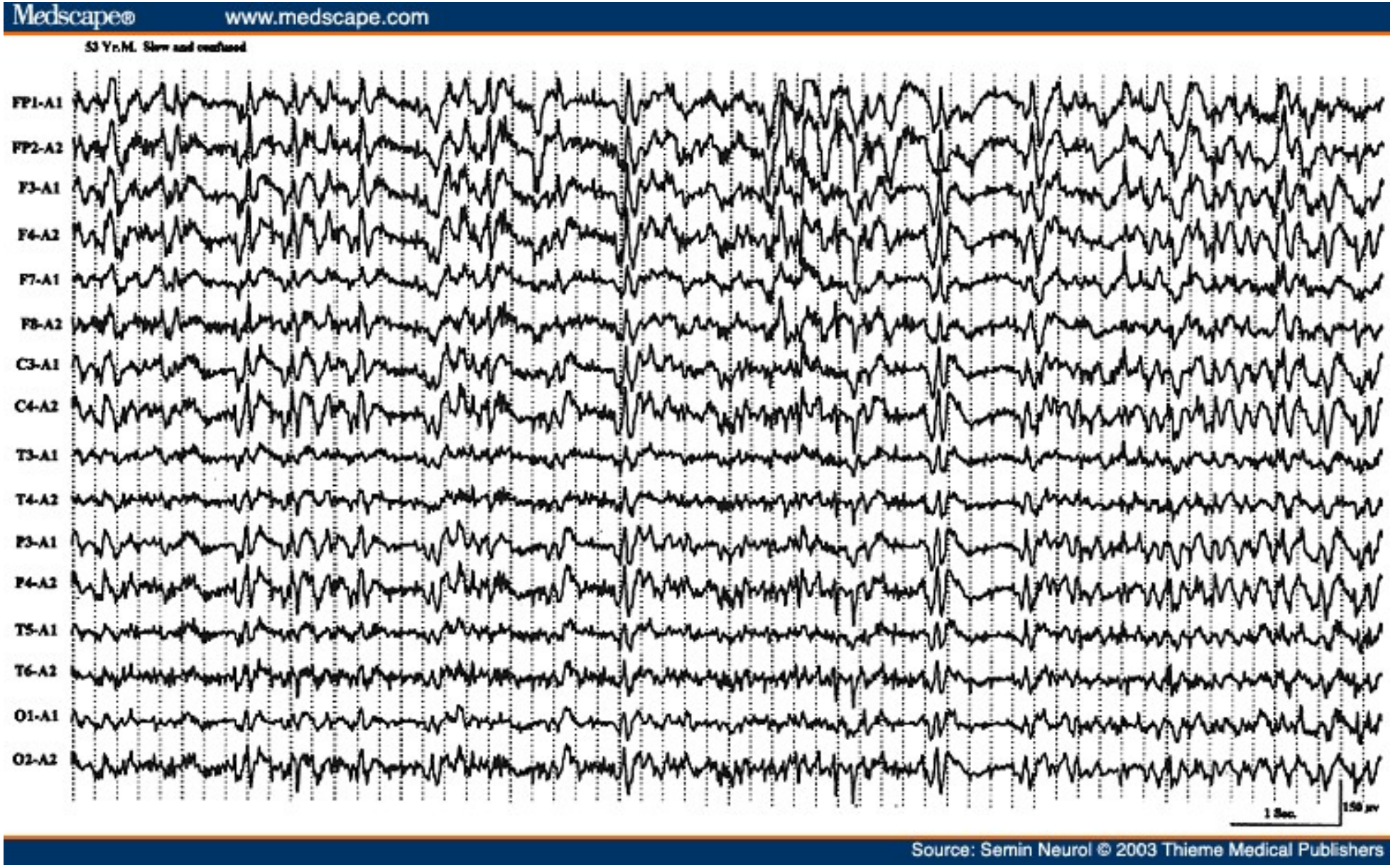
Genetic rodent models

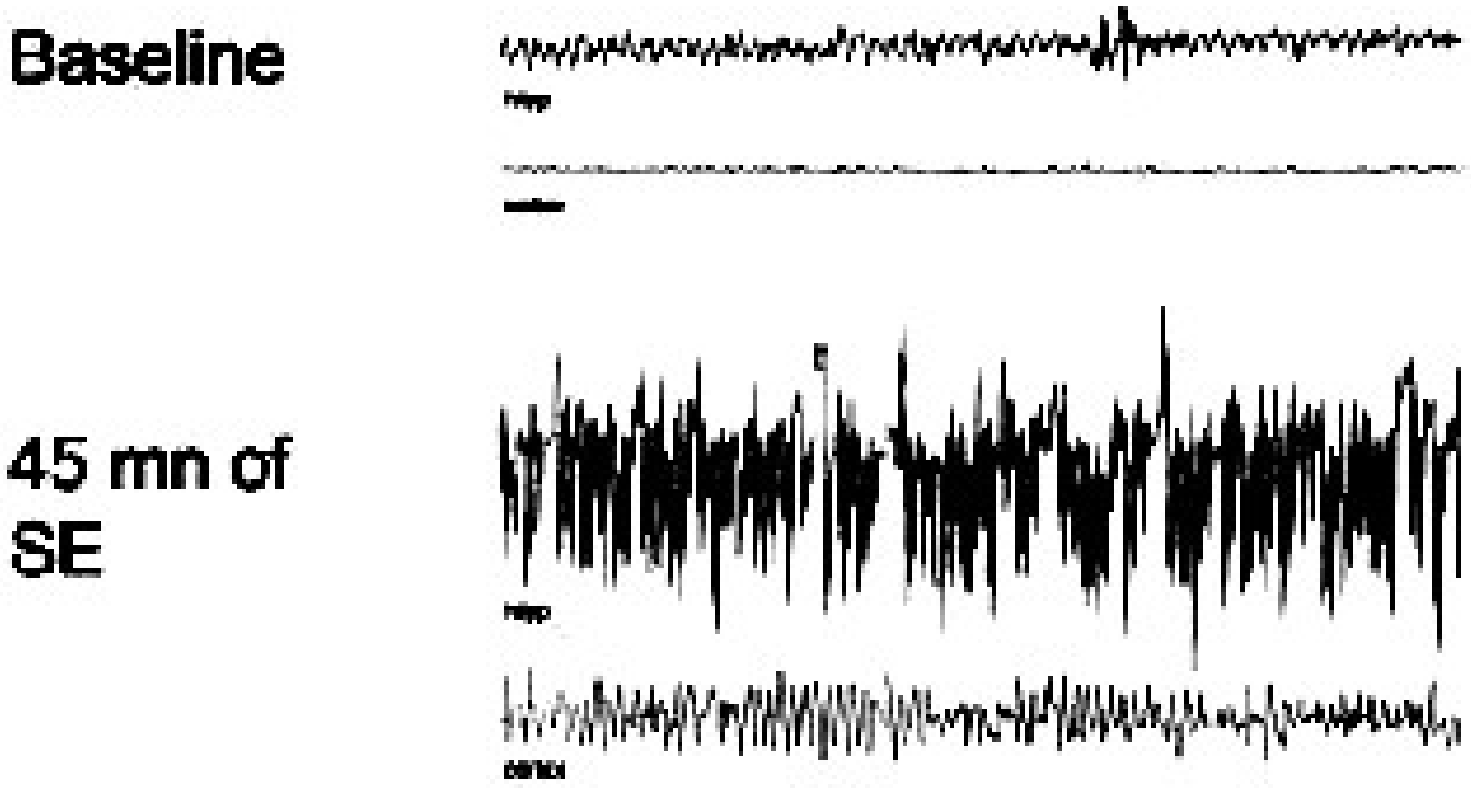
Status epilepticus

Lithium-pilocarpine

Human EEG in *status epilepticus*

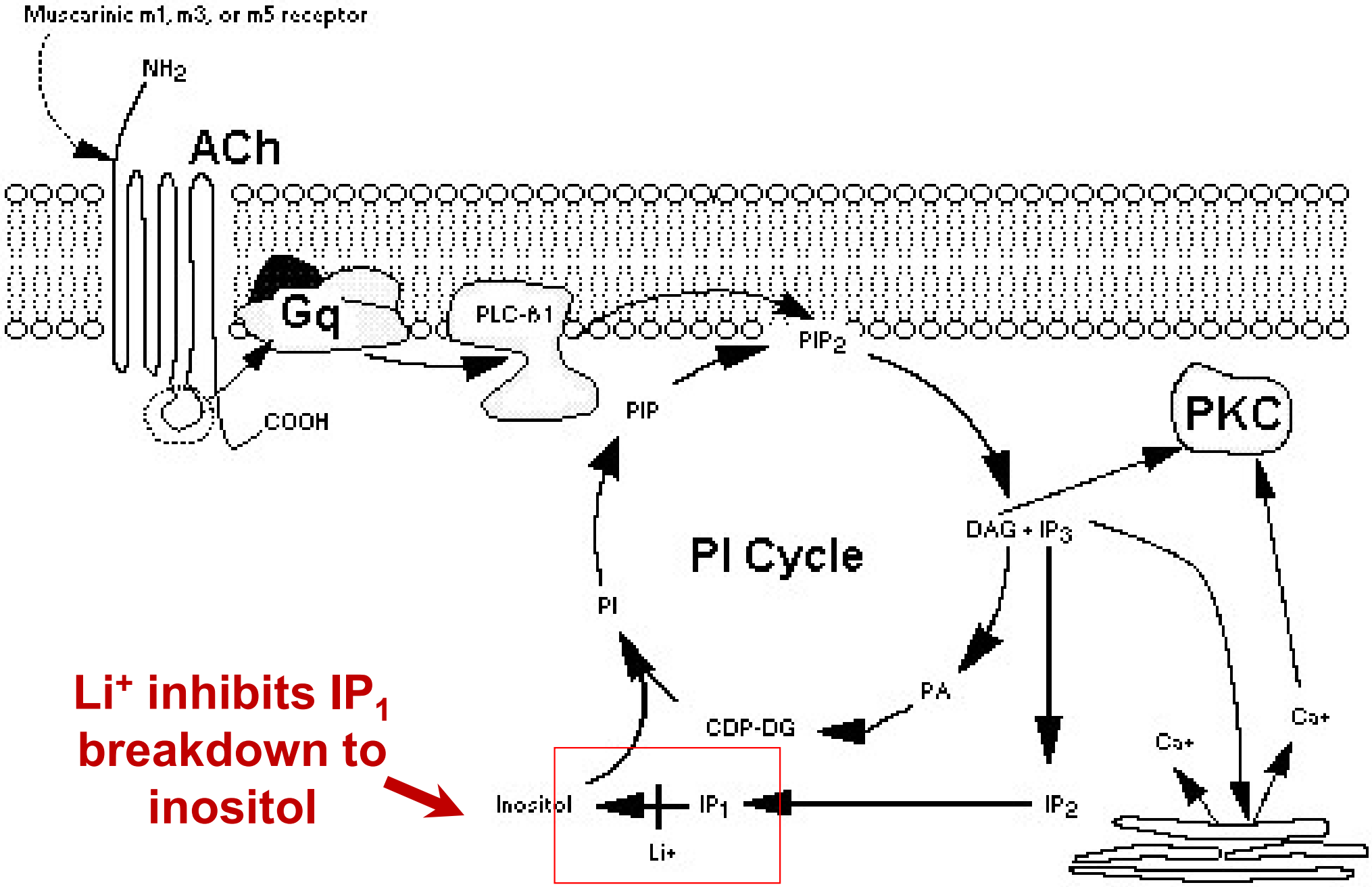


Li-pilocarpine model of *status epilepticus*



EEG patterns recorded in a Li-pilocarpine treated rat during *status epilepticus*

mAChRs stimulate membrane phospholipid turnover



Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Hyperthermia:	Experimental febrile seizures
Hypoxia:	Hypoxic-induced seizures
Traumatic brain injury (TBI):	Fluid-percussion brain injury
Stroke:	Vascular occlusion
Radiation:	*In utero* radiation exposure (model of cortical dysplasia); [γ-radiation-E17]
Dysplasia:	*In utero* exposure to methylazoxymethanol (MAM) produces a neuronal migration disorder similar to human cortical dysplasia

Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Models of pharmacoresistant epilepsy

Several *in vivo* animal models have also been developed that attempt to reproduce a phenotype that is consistent with **pharmacoresistant epilepsy,** an important and highly clinically relevant area: useful for testing new AEDs. These include:

- **The phenytoin - resistant kindled rat**
- **The lamotrigine- resistant kindled rat**
- **The low-frequency 6-Hz psychomotor seizure model of partial epilepsy**
- **The post-SE model of temporal lobe epilepsy (TLE)**

Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Models of pharmacoresistant epilepsy

The phenytoin-resistant kindled rat

Some populations of kindled animals display little or no response to a standard challenge dose of phenytoin, and are thus classed as **phenytoin 'non-responders**'. This is now regarded as a useful model of human patients that never become seizure free on phenytoin (and other AED) therapy and are thus considered to be drug-refractory.

The disadvantage of this model is that an extensive pre-screening progamme is necessary to identify the 'non-responder' animals.

Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Models of pharmacoresistant epilepsy

The lamotrigine-resistant kindled rat

Resistance to lamotrigine is developed by treating animals with a low dose of the drug during the kindling process. Ultimately, this leads to a reduced effectiveness of a higher dose of lamotrigine when it is tested in fully kindled animals. Interestingly, lamotrigine-resistant rats are also resistant to other AEDs ***e.g.* carbamazepine, phenytoin, topiramate;** nevertheless useful as a model for screening for novel effective drugs.

Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Models of pharmacoresistant epilepsy

The low-frequency 6-Hz psychomotor seizure model of partial epilepsy

This is similar to the MES electroshock model of generalized epilepsy but uses a **lower frequency** (6 Hz, *vs*. 50 Hz) delivered via corneal electrodes *vs*. trans-auricular (ear-clips). As stimulus current is increased, several AEDs lose their ability to protect against the induced seizure. Again, a fast, inexpensive and useful model for screening for novel anticonvulsant drugs.

Animal models of epilepsy

OTHER USEFUL ANIMAL EPILEPSY MODELS

Models of pharmacoresistant epilepsy

The post-SE model of temporal lobe epilepsy (TLE)

In this post-pilocarpine status model, the seizures that develop after a latent period, more resemble the human condition in that they are ***spontaneous,*** rather than evoked. It is considered a useful model for identifying more effective drugs for refractory complex partial seizures.

Conclusions

- **There are many animal epilepsy models** - epilepsy is a heterogeneous disorder - unlikely that one model would represent all the clinically observable forms.

- **All the epilepsy models have limitations:** - *i.e.* models give information on the mechanisms *of the models*, and not necessarily on the mechanisms of human the epilepsy! - because a model mimics a clinical seizure-type does not mean the underlying pathophysiology is the same! - ***Caution required in interpreting all animal model data.***

UCL School of Pharmacy