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**SEMMELWEIS
UNIVERSITY**



Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

Contributed by: Tamás Freund, Zsolt Liposits, Zoltán Nusser, László Acsády, Szabolcs Káli, József Haller, Zsófia Maglóczky, Nórbert Hájos, Emilia Madarász, György Karmos, Miklós Palkovits, Anita Kamondi, Lóránd Eröss, Róbert Gábel, Zoltán Kisvárdai, Zoltán Vidnyánszky

Epilepsy and neurodegenerative disorders

Imre Kalló & Zsófia Maglóczky

Pázmány Péter Catholic University, Faculty of Information Technology

- I. Epilepsy as a disease.
- II. Functional morphological changes in the epileptic hippocampus.
- III. Experimental models of epilepsy.

Functional morphological alterations in epileptic diseases: cell death and reorganisation



EPILEPSY: It is a chronic functional disturbance characterized by spontaneously recurrent seizures and different etiology.

FUNCTIONAL BACKGROUND: Large number of cells fire synchronously.

EPIDEMIOLOGY: About 2% of the population is affected.

MOST FREQUENT: Focal epilepsy with temporal lobe origin (TLE).

Questions arise:

What is the mechanism of the synchronous discharges?

What is the structural basis of this functional disturbance?

Classification of epileptic fits

1. Partial (focal, local) fits

- simple partial seizures (no disturbance of consciousness)
with motor, somatosensory, autonomic, psychic symptoms
- complex partial fits (there is disturbance of consciousness)
it may start with a simple partial onset, which is followed by
the disturbance of consciousness with automatisms or it is
dominated by the disturbance of consciousness from the beginning

THEY CAN GENERALISE SECONDARILY

2. Generalized fits

- absence (with disturbance of consciousness) (PM) it may be accompanied by
automatism, clonus, atonia, tonus, autonomic components
- tonic-clonic seizures, (GM) (only tonus, only clonus, only atonia)
- myoclonus (involuntary muscle contractions, localised or generalised,
upper limb is more frequently affected)

3. Non-classified seizures

- e.g. febrile seizure

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Etiology of epileptic seizures

- perinatal anomalies
- brain injury (infarcts)
- tumor, pressure injury of the brain, head trauma
- unknown reason
- neuronal infection
- vascular malformation
- developmental malformation of the nervous system (dysplasia, migrational disturbances, microgyria, heterotopia etc.)
- genetic errors
- intoxications (alcohol, medicines, drugs, herbicides etc.)

Cortical and temporal epilepsy is often accompanied by developmental malformations – dual pathology

Malformation of Cortical Development (MCD)

Types of MCD

- proliferation-related (reduced, increased, time-shifted)
- migration-related (e.g. heterotopia)
- organization-related (polimicrogyria, microdysgenesis, schizencephalia)
- others

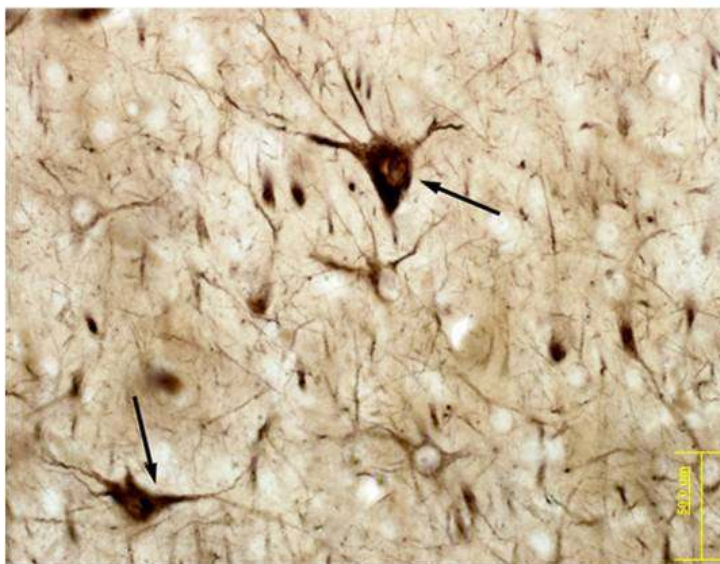
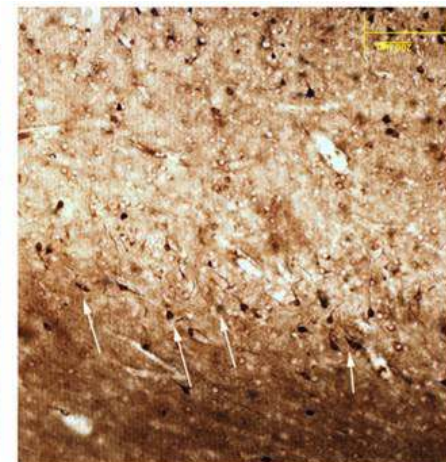
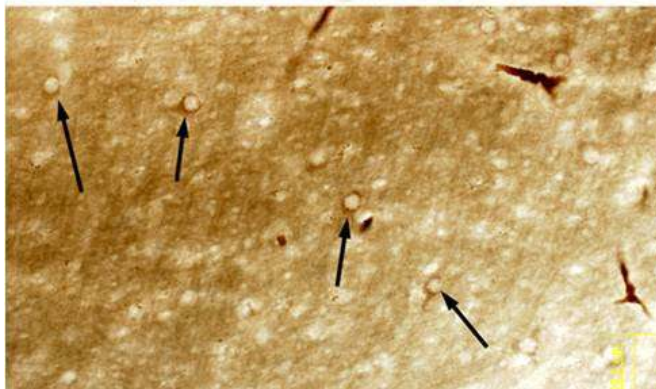
Focal appearance: Focal Cortical Dysplasia (FCD)

Ectopic neurons, immature neurons, giant cells, abnormal layer formation

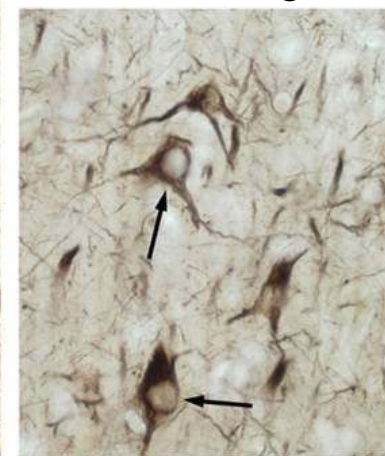
In general, there are fewer inhibitory cells in MCD, consequently its epileptogenic state is hypothesized!

Frontal focal dysplasia

Cells in the white matter



Hypertrophic neurons
SMI 32 staining



Epilepsy as a disease



Epilepsy is frequently accompanied by other psychiatric diseases:

depression, psychotic symptoms, personality changes, decay of cognitive capabilities, anxiety, increased rate of suicides etc.



Treatment for epilepsy

There is no causal therapy.

Either patients get over the epilepsy
„spontaneously”

Or receive treatments, which aim to
prevent seizures.

- antiepileptic drug treatment
- antiepileptic surgery



Antiepileptic surgery

It is recommended only, if the source of the epileptic seizure (the focus) is known.

Most frequently the temporal lobe is targeted, and portions are removed such as the hippocampus, subiculum, entorhinal cortex or temporal cortex.

Antiepileptic surgery

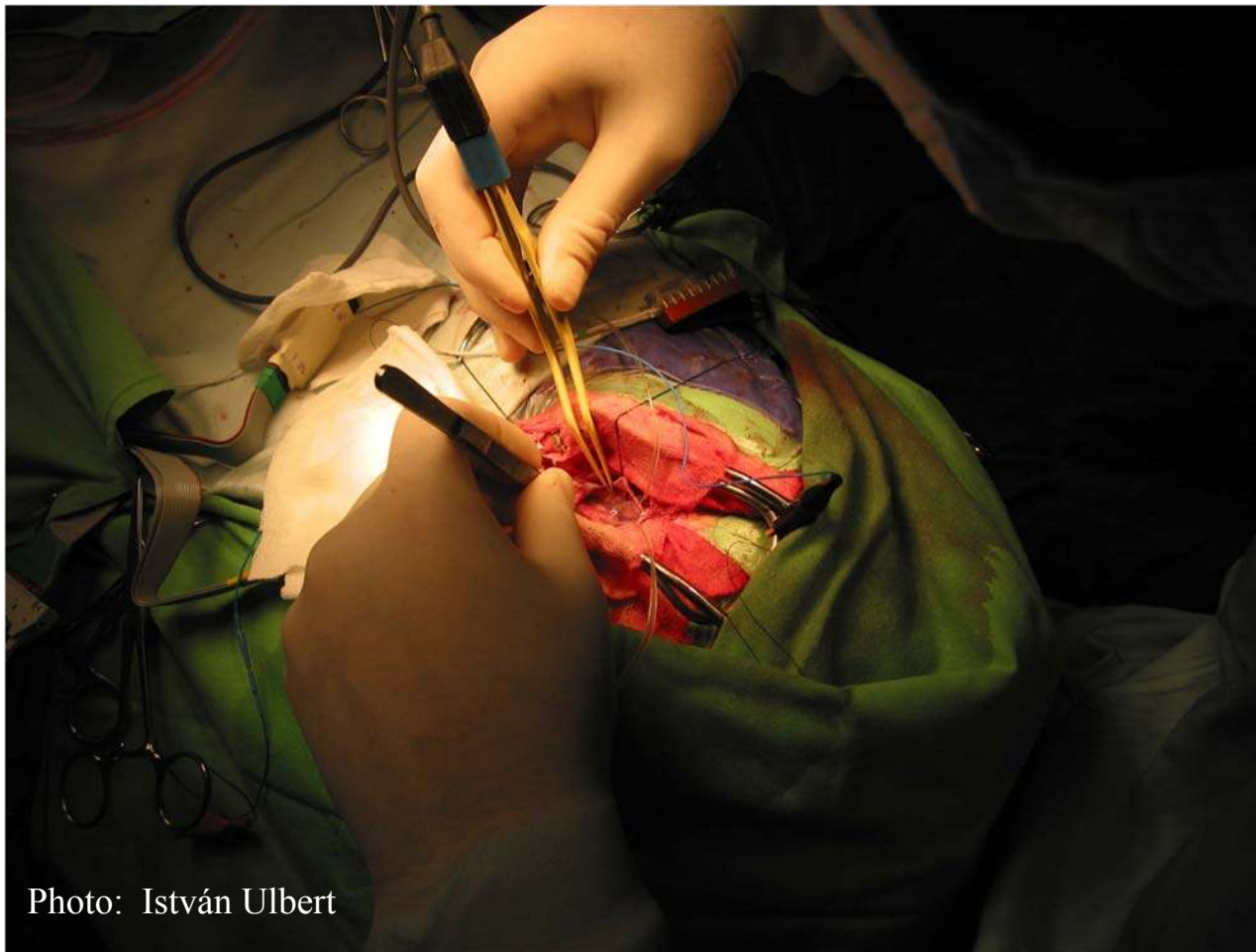


Photo: István Ulbert

In case of focal epileptic seizures and drug therapy resistant epilepsy, the epileptic focus can be removed.

Localization of the epileptic focus

- Focus in the cerebral cortex:

Usually it is associated to developmental abnormalities e.g. dysgenesis, dysplasia, migrational disturbances, abnormal gyrification, etc .

-Focus in the temporal pole:

Affected areas are the hippocampus, amygdala, subiculum, entorhinal, perirhinal, piriform cortices, temporal cortex, insula.

The focus can be one of these regions, or even more of them.

Sometimes the focus migrates from one place to the other. Dual pathology is also possible, e.g. when the focus is in the entorhinal cortex, the subiculum or the amygdala, dysplasia or minor abnormalities might be also present in cortical areas.

-Tumor may also cause seizures

- Febrile seizure, head trauma may also cause recurrent seizures

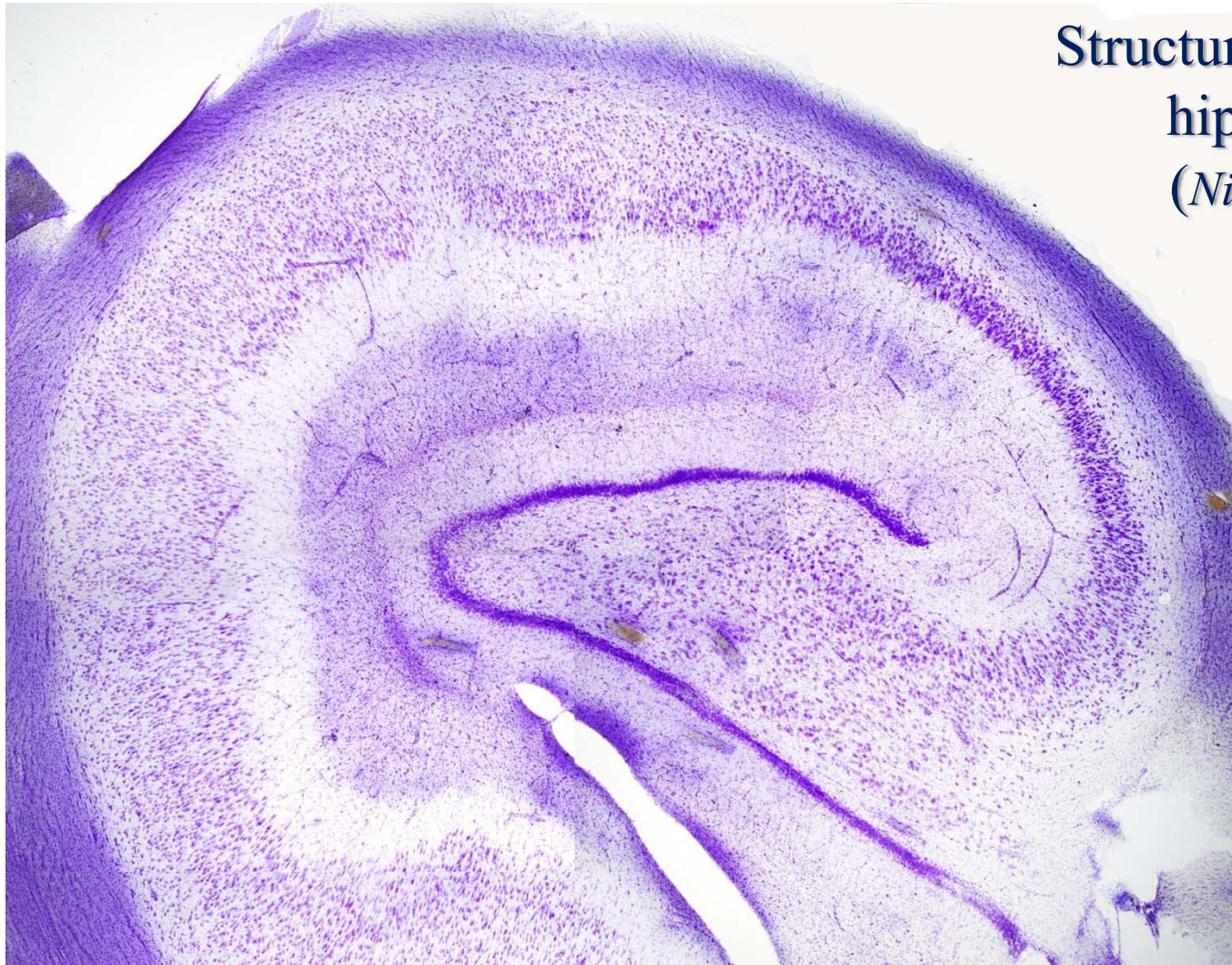
Functional neuromorphological studies on the epileptic reorganisation of the hippocampus sampled from patients with temporal lobe epilepsy

Most frequently affected brain region is the hippocampus, which is partially removed from the brain of drug therapy resistant patients.

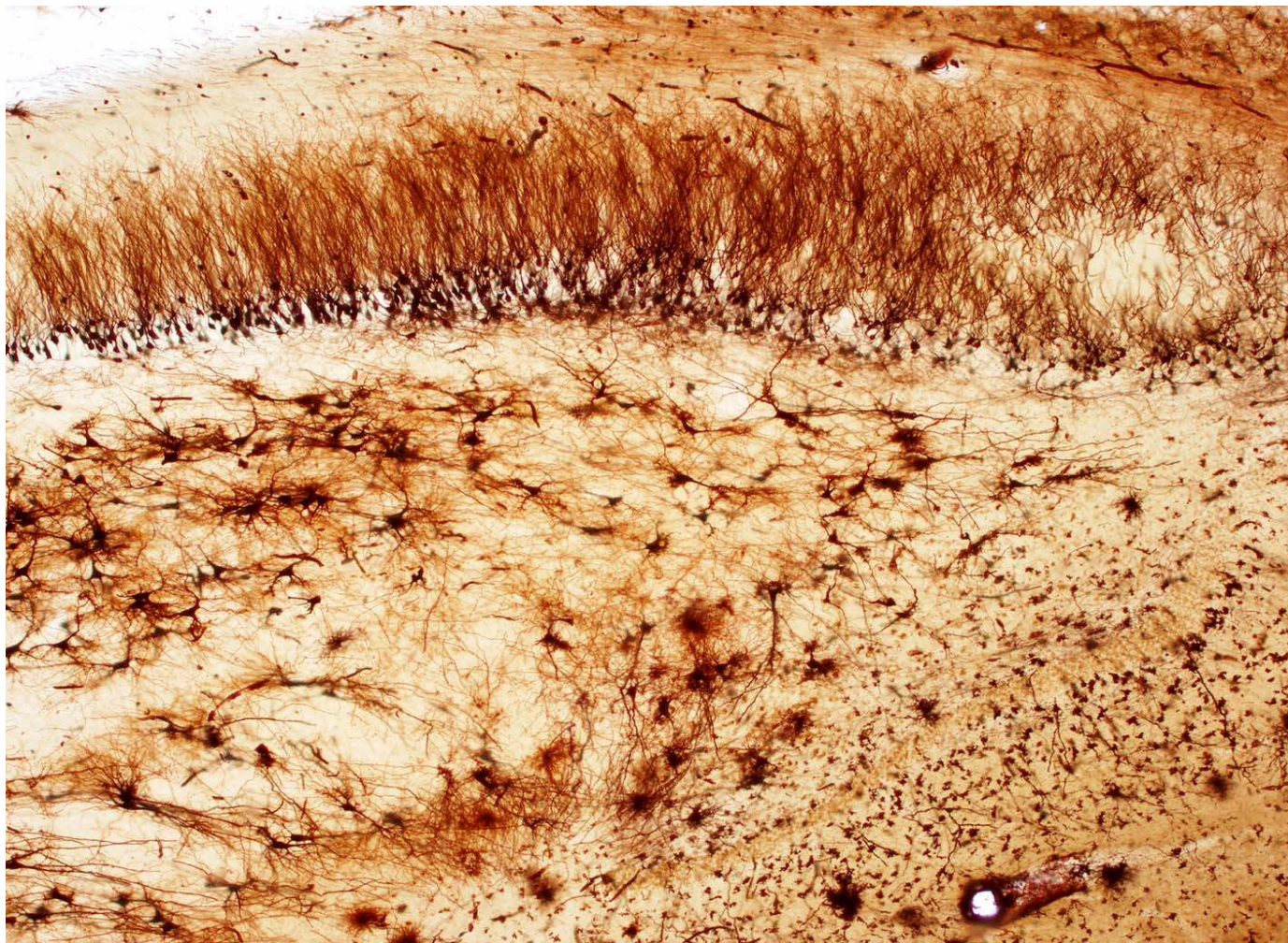
Molecular biological, cellular and/or neuronal network studies (licenced!) can be carried out on the tissue samples removed.

Levels of epileptic reorganisation

- Intracellular changes (receptors, ion channels, gene transcription, second messenger systems, enzyme activity, cellular organelles etc.)
- **Cellular events (cell death, cell division, cell migration, morphological deformations, gliosis, quantitative and qualitative alterations in neurochemical markers)**
- **Changes at neuronal network level (changes of intercellular connections, axonal decay/ sprouting)**
- Changes in the activity of cells/cell groups
- Alterations in large pathways connecting brain regions (decay or sprouting in neuronal pathways)
- Changes affecting the whole CNS (hormonal or metabolic alterations, synthesis/degradation of neurotransmitters, changes in the EEG pattern etc.)



Structure of the human
hippocampus
(*Nissl-staining*)



Golgi-staining, human dentate gyrus

Camillo Golgi
(1843-1926)

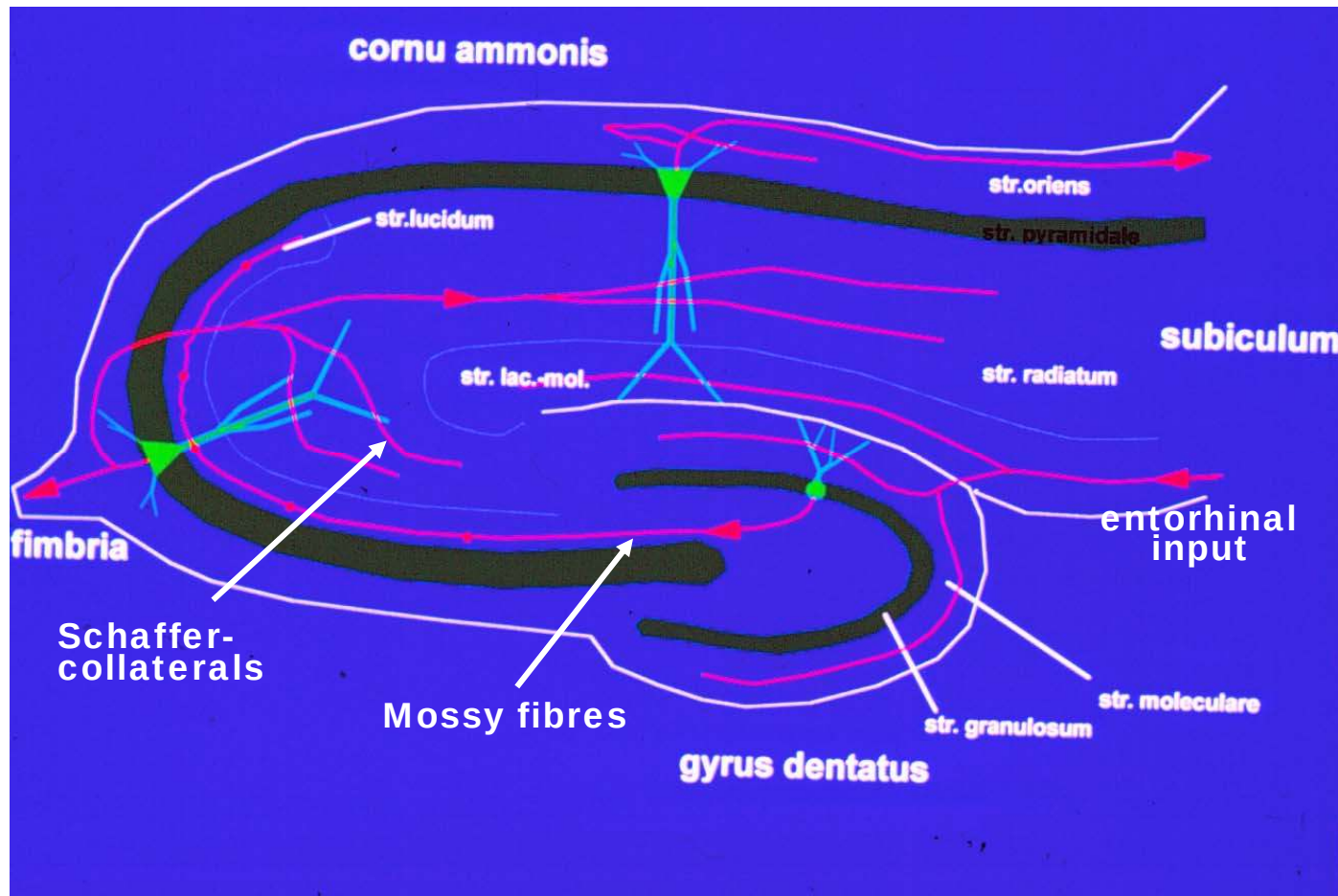
1873: discovery of
staining

1906: Nobel prize,
shared with
Ramon y Cajal

Golgi-staining, human gyrus dentatus, granule cells



The hippocampal trisynaptic loop

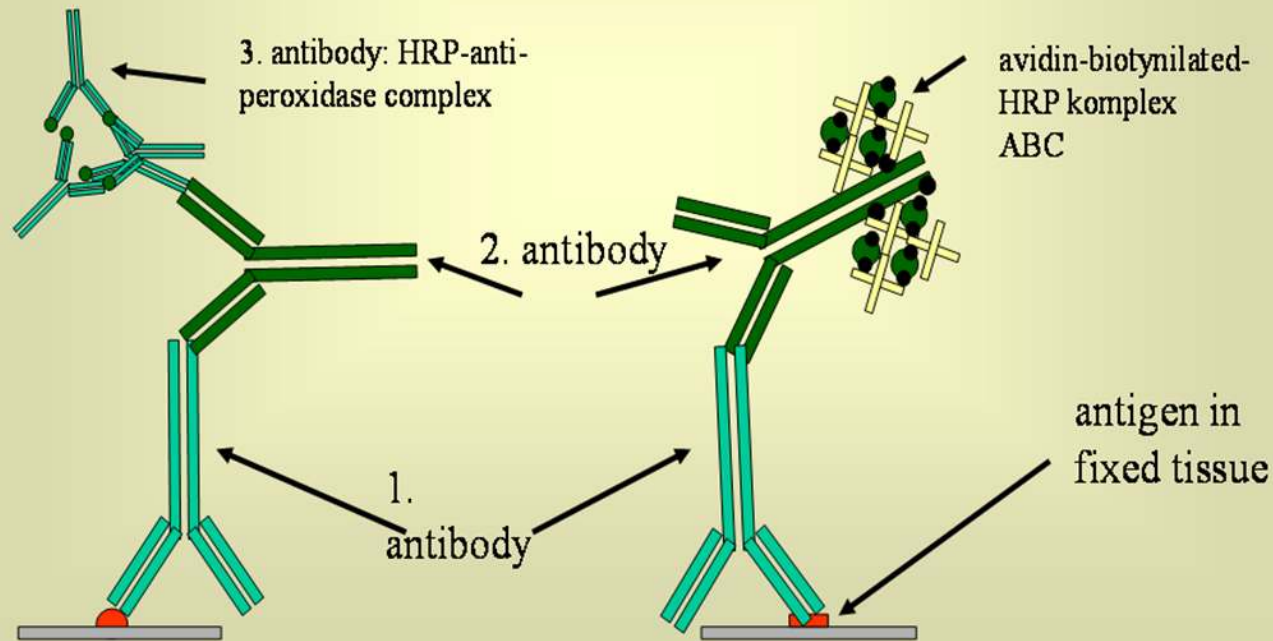


3-step immunostaining applied in the studies

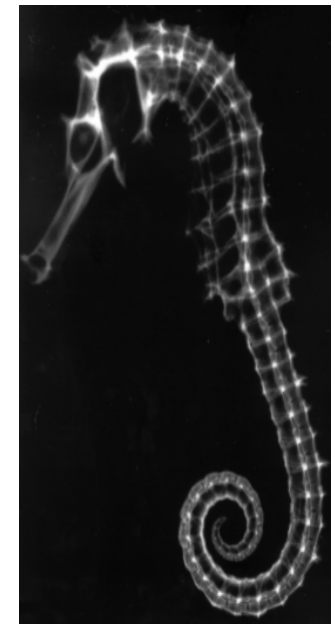
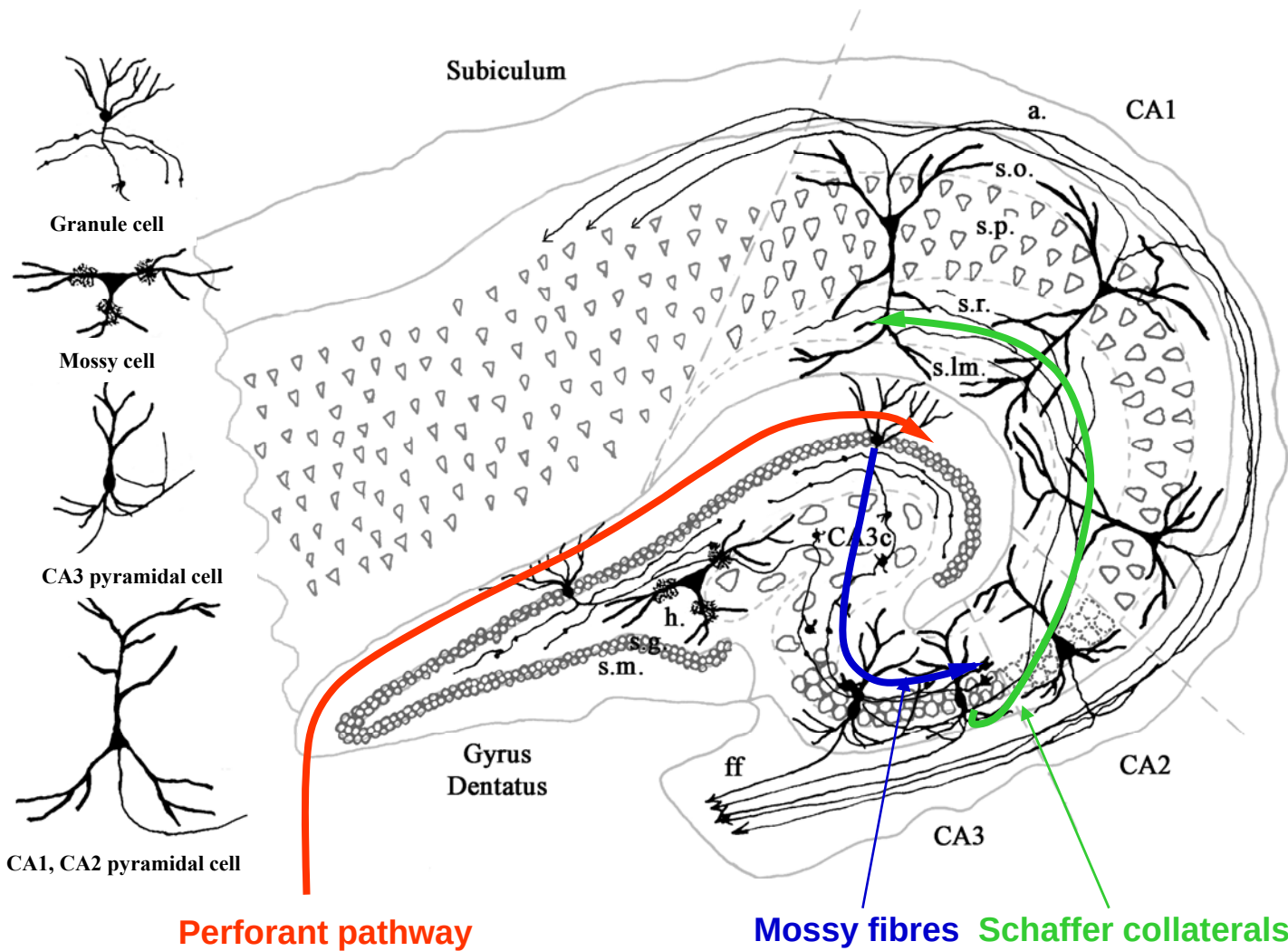
PAP (Peroxidase anti-peroxidase)

ABC (avidin-biotynilited HRP)

Chromogene: diaminobenzidin, (DAB). The horseradish peroxidase enzyme (HRP) produces free 'O' from H_2O_2 . Free 'O' reacts with DAB. Dark precipitation is formed around the antigen.



Principal cells (human control tissue)



Drawing was made by Lucia Wittner (PhD thesis, 2004)

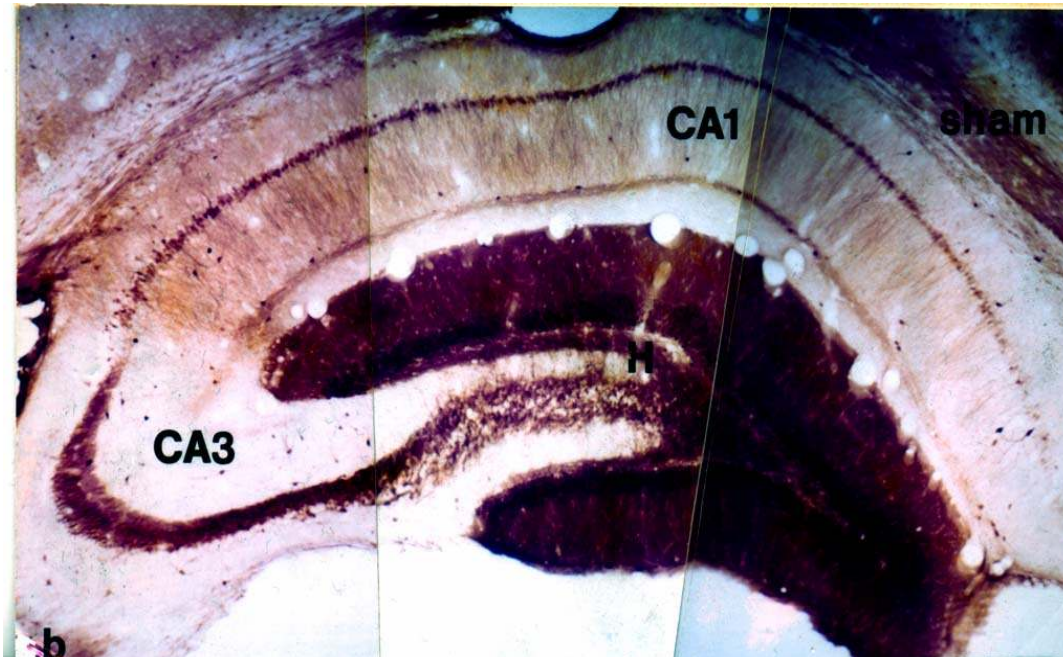
Principal cells of the hippocampus

Blue:RAT. RED: HUMAN. BLACK: BOTH

AREA	PRINCIPAL CELL	TRANSMITTER	NEUROCHEMICAL MARKER
Cornu Ammonis-CA1	Pyramidal cell	glutamate	Calbindin, GluR2/3-R, NeuN
CA2	Pyramidal cell	glutamate	Calbindin, GluR2/3-R, NeuN
CA3	Pyramidal cell	glutamate	GluR2/3-R, NeuN
CA3c	Pyramidal cell	glutamate	GluR2/3-R, NeuN
Hilus	Mossy cell	glutamate	CART peptide , GluR2/3-R CGRP , (calretinin in mouse, partially in monkey)
Gyrus dentatus	Granule cell	glutamate, GABA (No GABA transporter)	Calbindin, GluR2/3-R, Dynorphin, CART peptide , NeuN

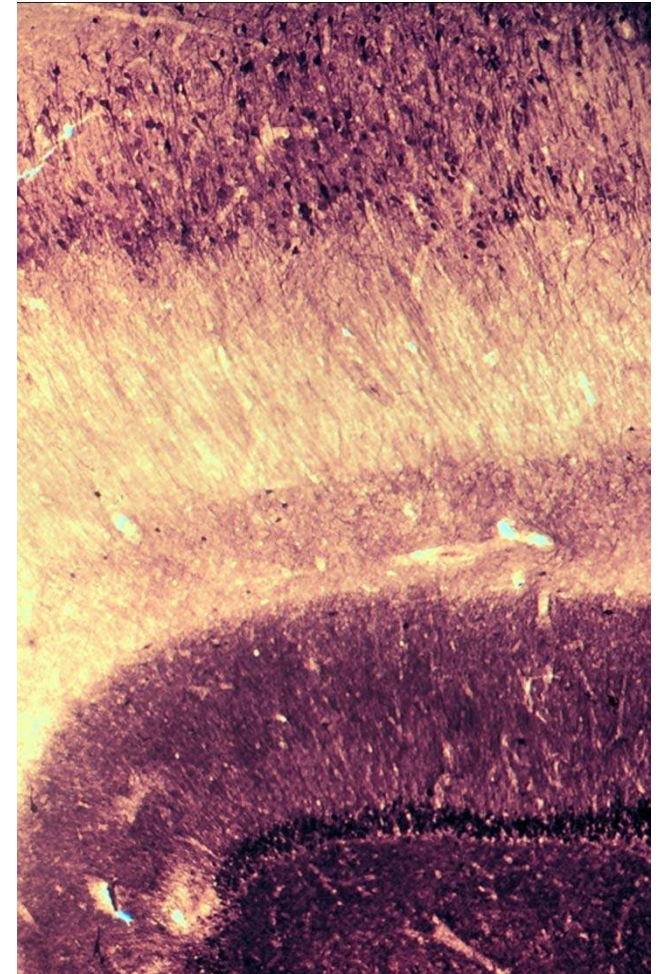
Common neurochemical features

Granule cells, CA1 and CA2 pyramidal cells are CB-immunoreactive
rat

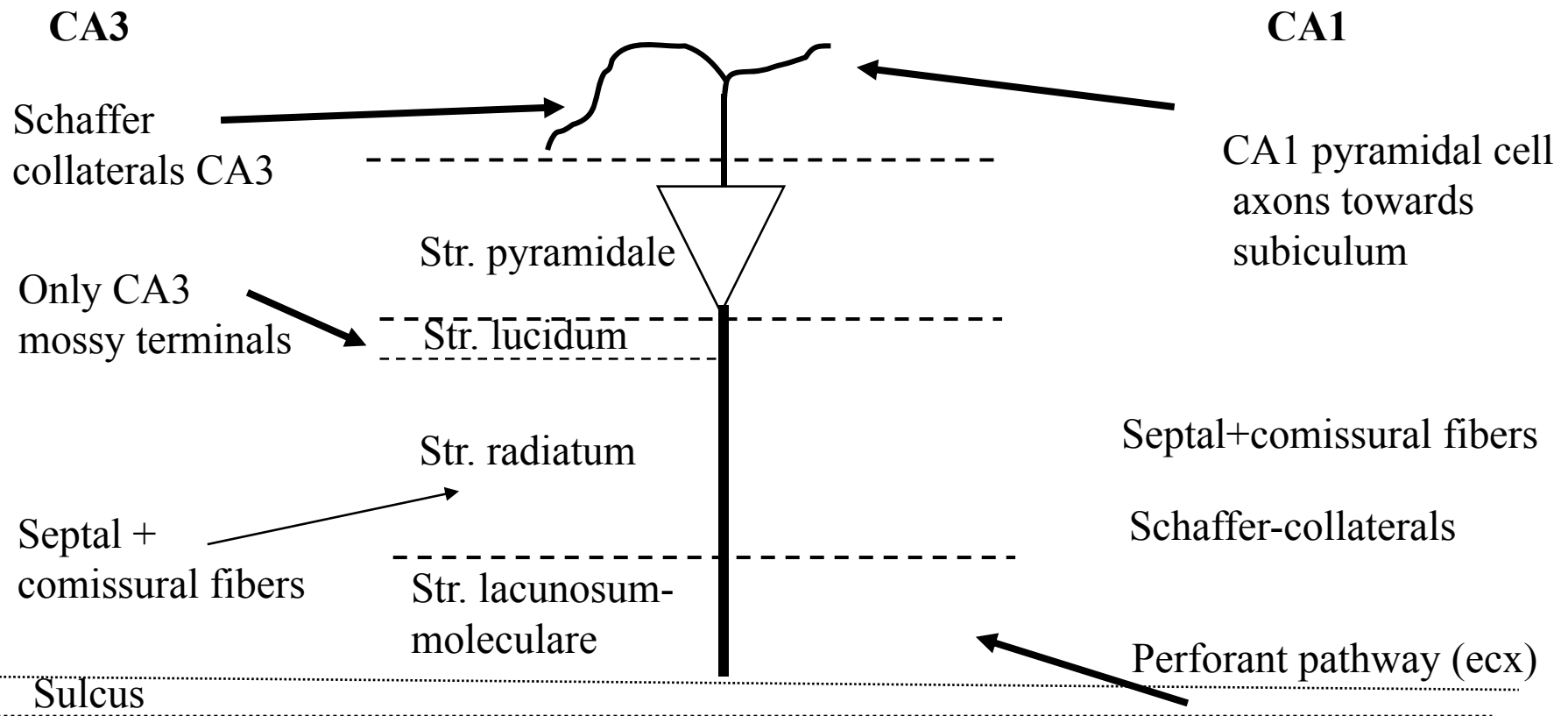


Calbindin-immunostaining

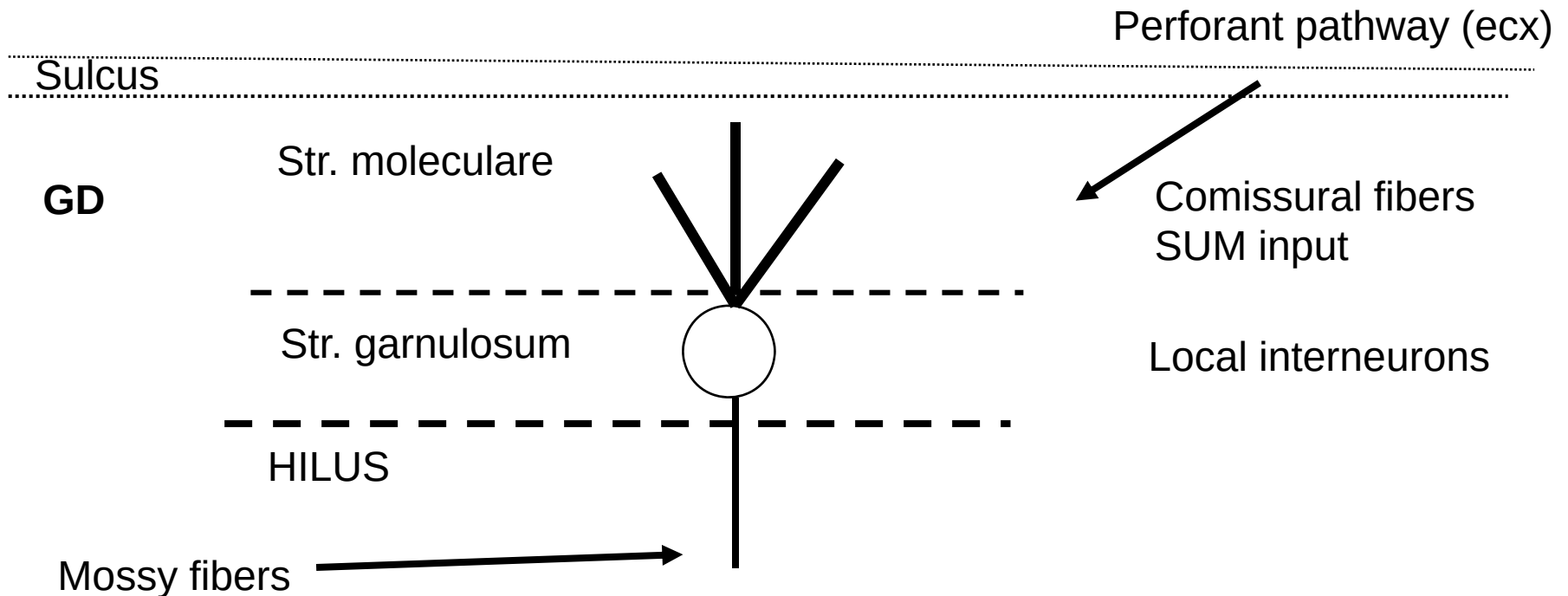
human



Layer-specific input of principal cells – pyramidal cells

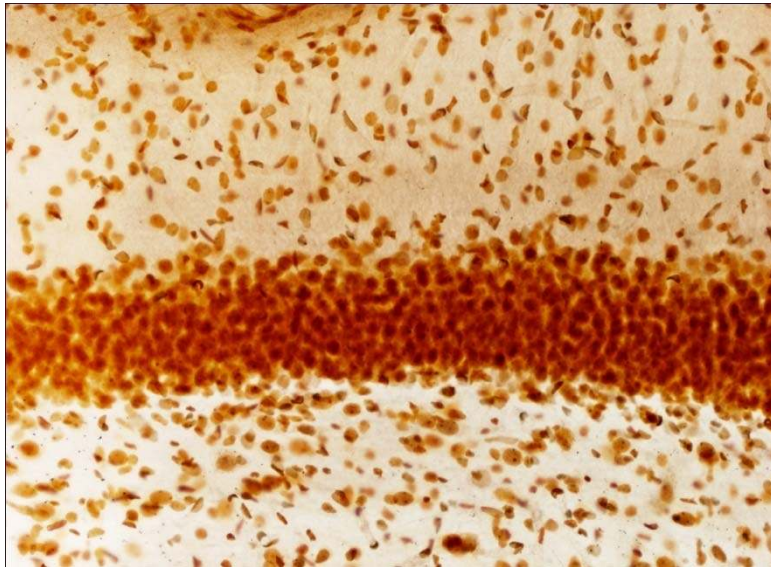


Layer-specific input of principal cells – granule cells



Granule cells

rat



Mossy terminals

15-20 terminals

30-50 active zones

there are no recurrents

Acsády et al. , 1998, J. Neurosci

human



Basal dendrites in the hilus 20%

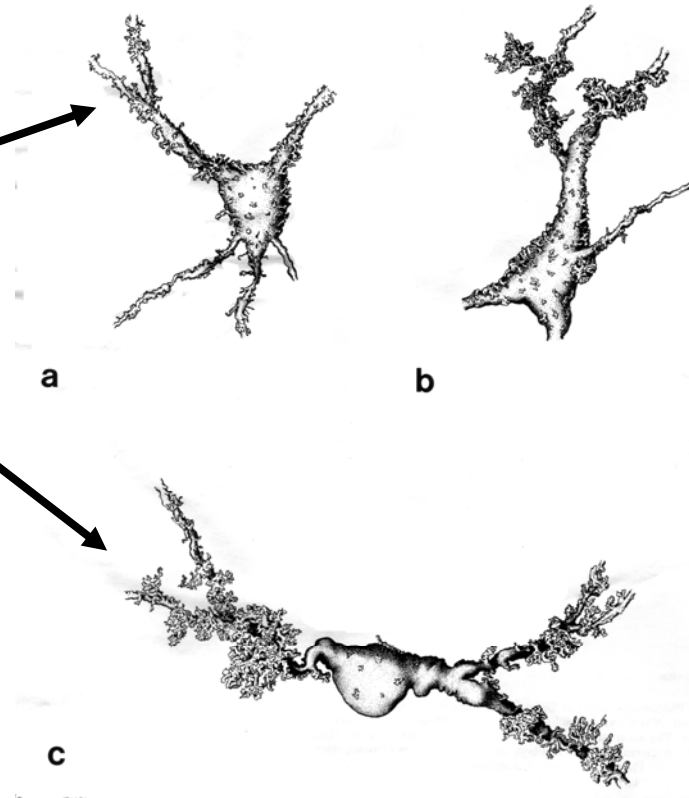
Seress & Ribak, 1992, Brain Res.

Mossy cells

136 HIPPOCAMPUS VOL. 2, NO. 2, APRIL 1992

**Complex
spines**

(mossy fibers
terminate on it)



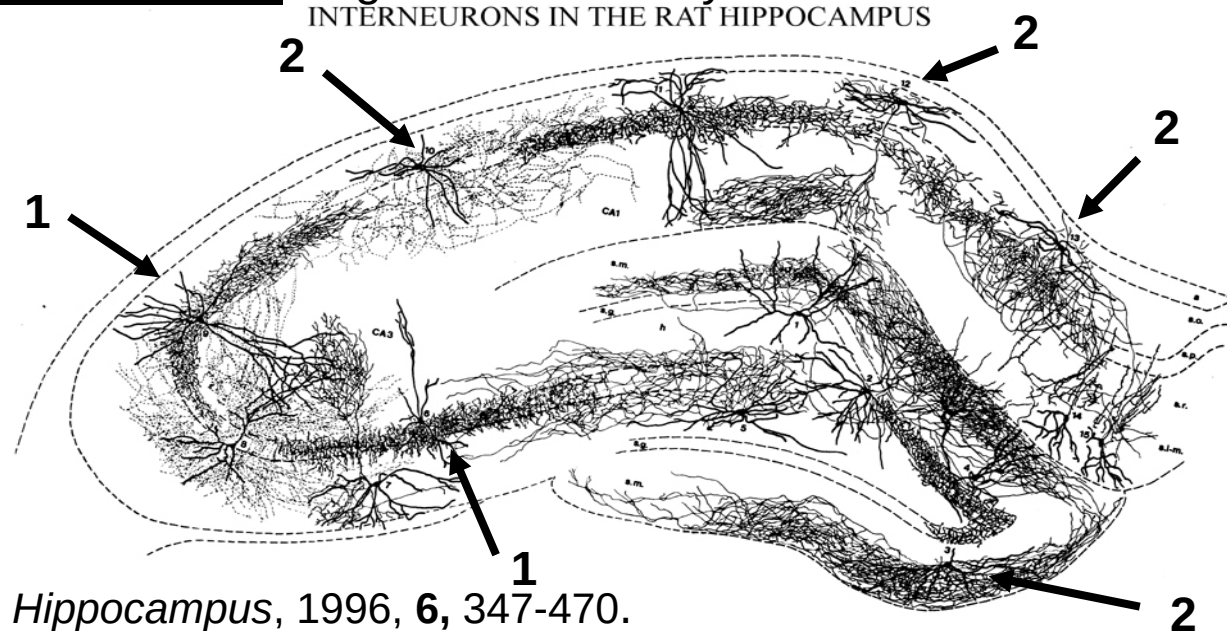
developing

adult

Seress L. *Az emberi hippocampus születés utáni fejlődése.*
Lege Artis Medicine, 2000. 10 (6):489, 5. ábra

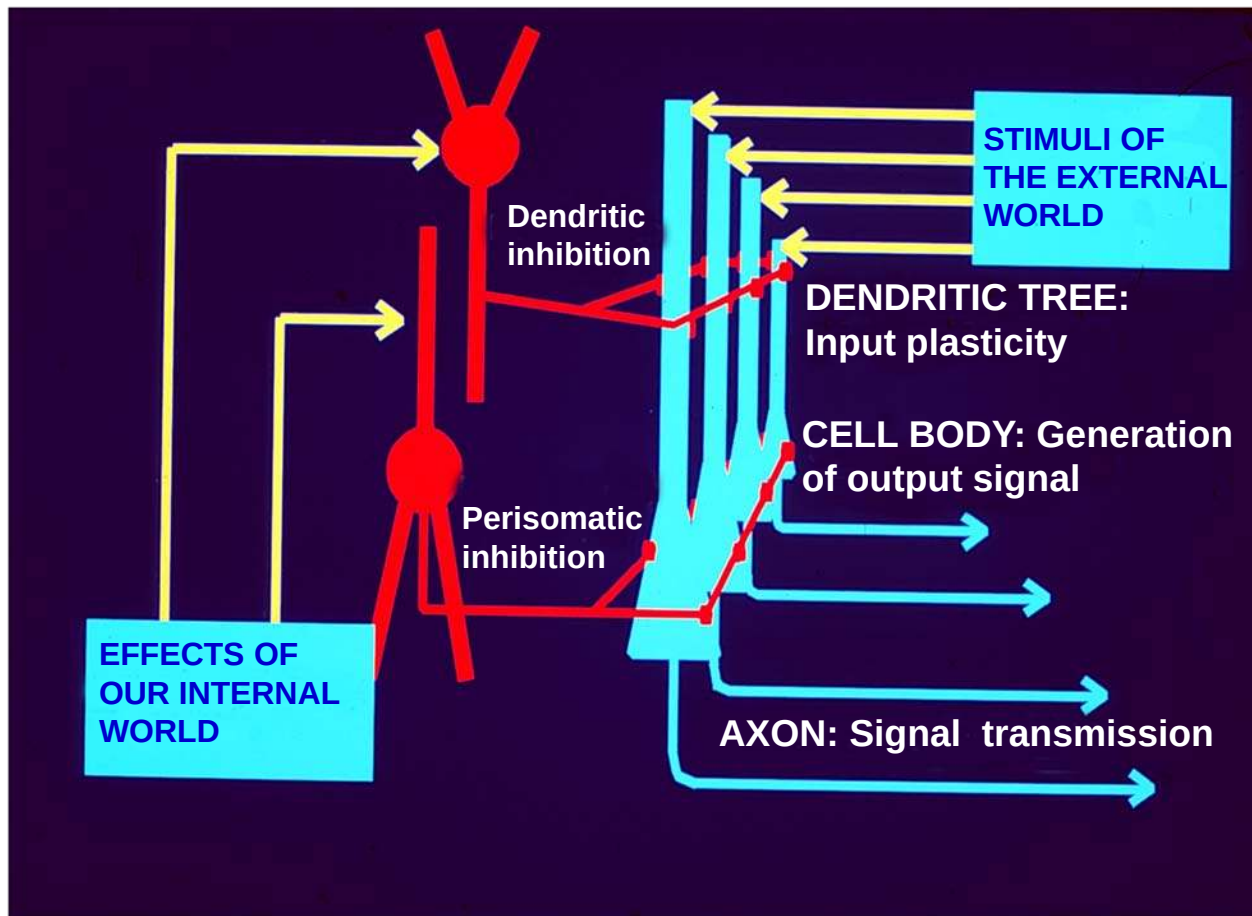
Functional types of inhibitory cells according to their targets

1. **Perisomatic inhibitory cells**: terminate on principal cells bodies, proximal dendrites and axon initial segments; regulate the output activity (basket and chandelier or axo-axonic cells)
2. **Dendritic inhibitory cells**: terminate on distal dendrites of principal cells; regulate the input activity
3. **Interneuron selective cells**: regulate the activity of interneurons



Freund and Buzsaki, *Hippocampus*, 1996, **6**, 347-470.

Role of dendritic and perisomatic inhibition

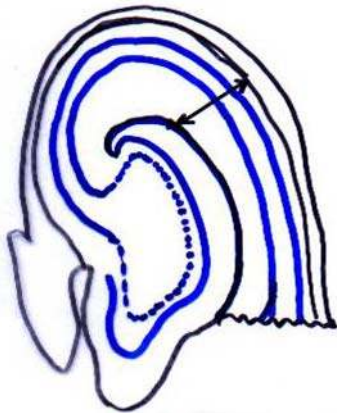


Function of neurochemically different inhibitory cells in the human hippocampus

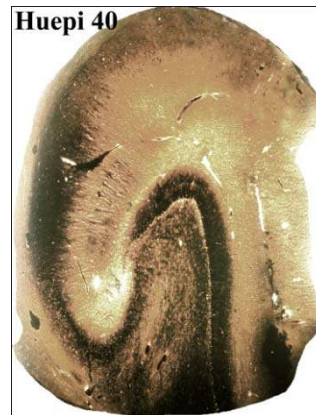
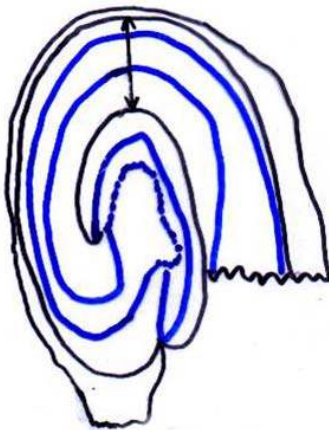
Red: calcium binding proteins; Blue: neuropeptides; Orange: receptor

Parvalbumin-containing interneurons	basket and axo-axonic cells, perisomatic inhibition (+ any species examined)
Calbindin-containing interneurons	dendritic inhibition , + axo-axonic cell, perisomatic inhibition (rat: only dendritic)
Calretinin-containing interneurons	Dendritic and interneuron specific inhibition (rat: different)
Cholecystokinin-containing interneurons	Perisomatic and dendritic inhibition (+rat)
Somatostatin-containing interneurons	Dendritic inhibition (+rat)
Neuropeptid Y-containing interneurons	Dendritic inhibition (+rat)
Substance P receptor expressing interneurons	Dendritic inhibition (rat: different)

Pathological types of TLE patients regarding the principal cell loss

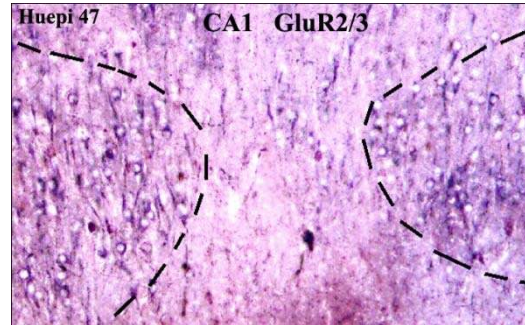


Control

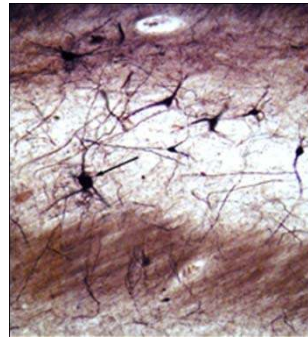


**1: “mild” group,
similar to the control**

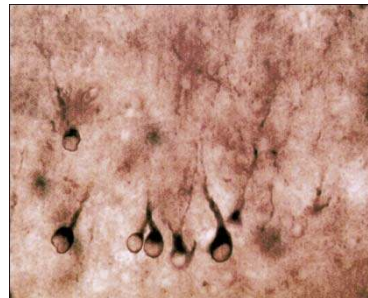
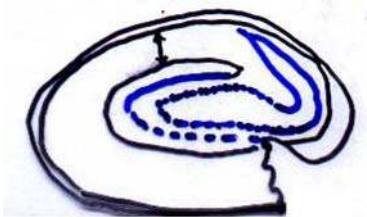
Pathological types of TLE patients regarding the principal cell loss



2: “patchy” type
patchy pyramidal cell loss



3: “sclerotic” type
Profound CA1 pyramidal cell loss

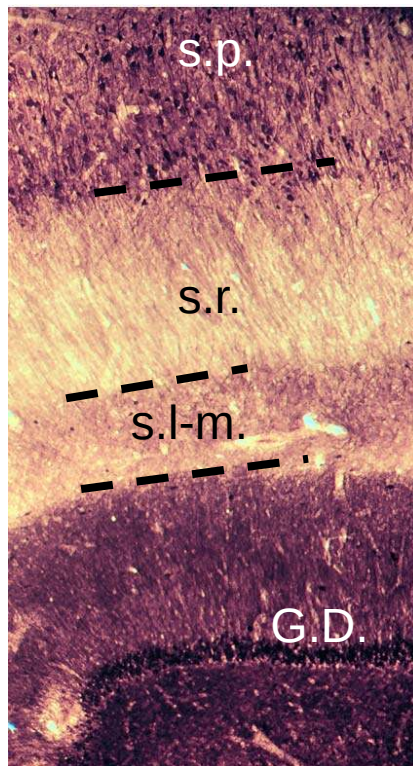


4. “gliotic” type
loss of all cell types including
the resistant cells
(granule cells, CB-
immunostained interneurons)

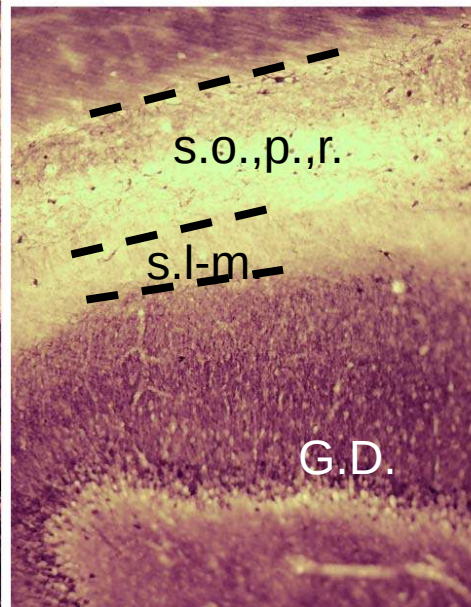
Hippocampal sclerosis

so: stratum oriens; **sp**: stratum pyramidale;
sr: stratum radiatum; **sl-m**: stratum
lacunosum-moleculare; **DG**: dentate gyrus

Control CA1



Epileptic CA1

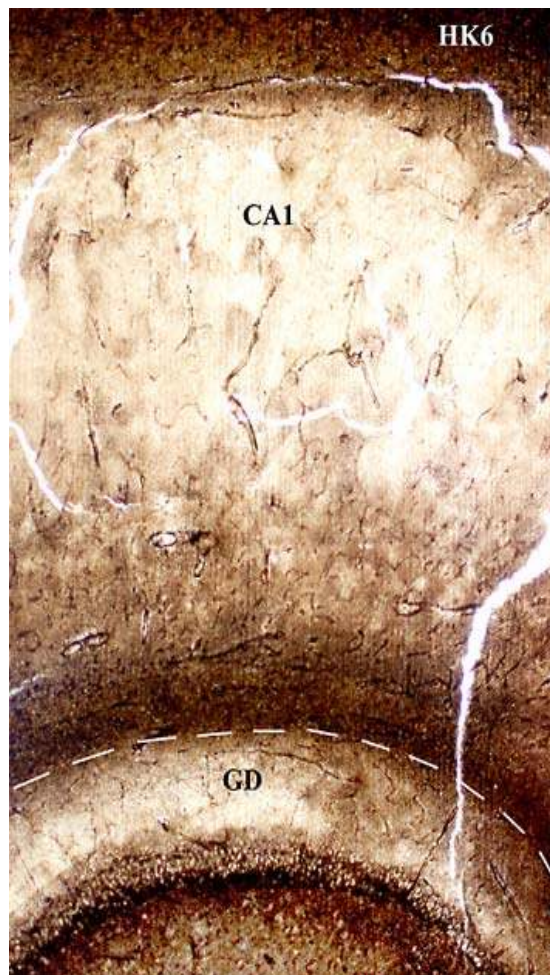


Calbindin-
immunostaining

Huepi 75



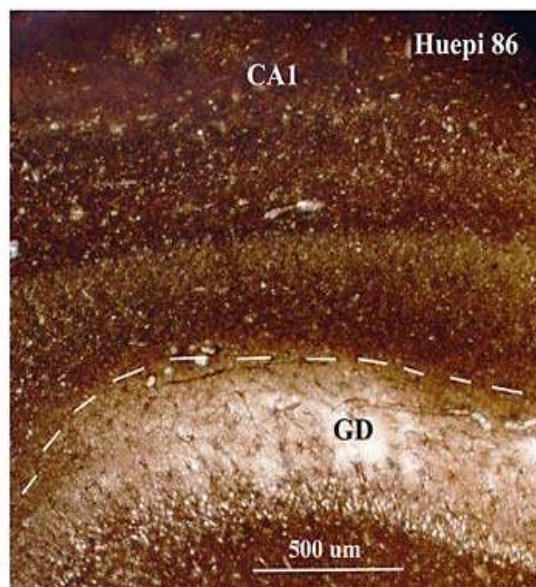
Control



Gliosis

The amount of glial fibers increases significantly in the hippocampus of epileptic patients. Gliosis is very characteristic for the sclerotic CA1 region, and also present in the dentate gyrus. GFAP immunostaining.

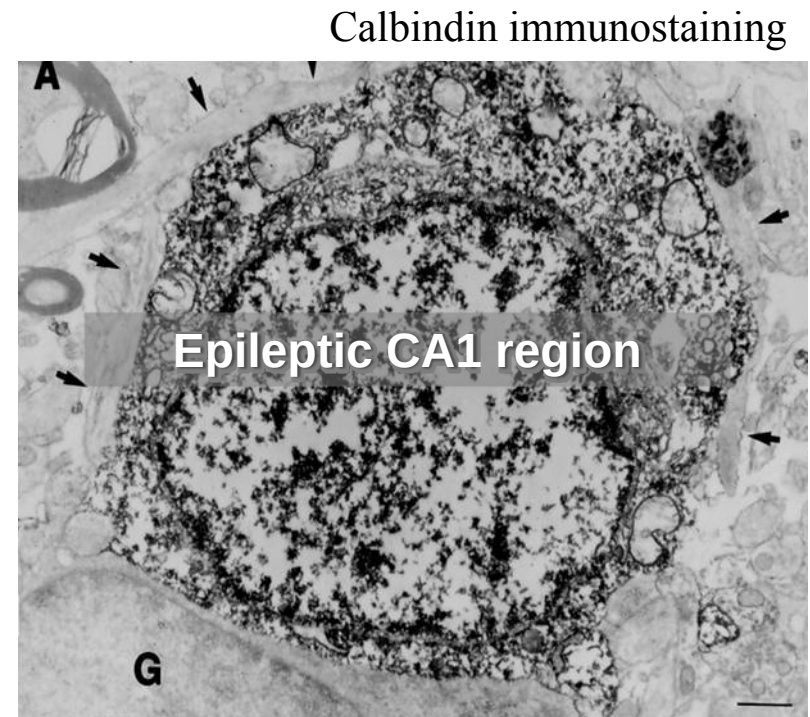
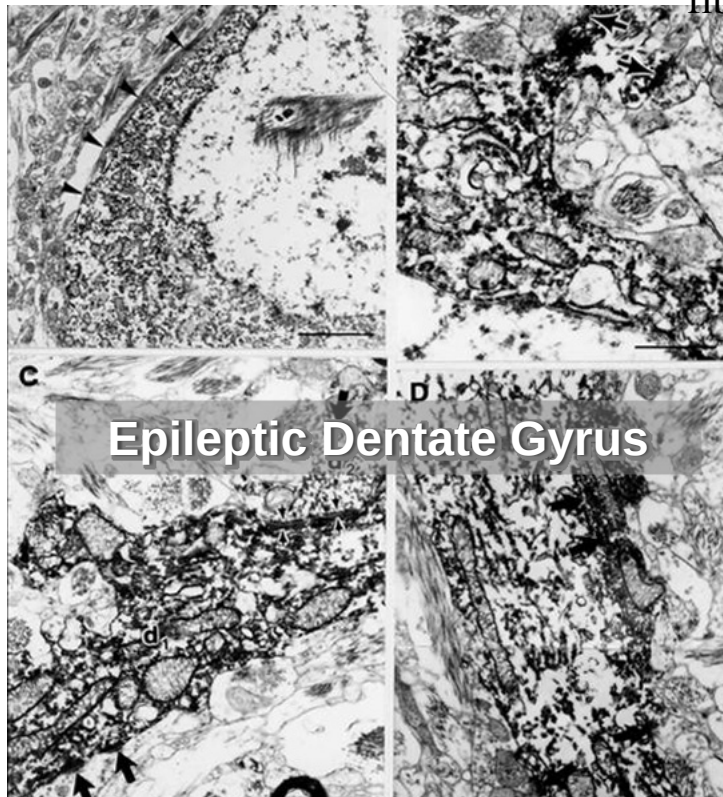
Epileptic, sclerotic



Maglóczy Zs: A hippocampális neuronhálózatok átalakulása krónikus temporális lebeny epilepsiában.
In: Halász P (ed.)
Hippocampus, mint neuropszichiátriai betegségek közös nevezője.
Budapest: Melinda Kiadó,
2005. pp. 61-101.

Glios

The amount of glial fibers increases significantly in the hippocampus of epileptic patients. Large amount of glial fibres is very characteristic for the sclerotic CA1 region, and also present in the dentate gyrus. There is also increased amount of glial fibers visible in the hippocampus of non-sclerotic patients.

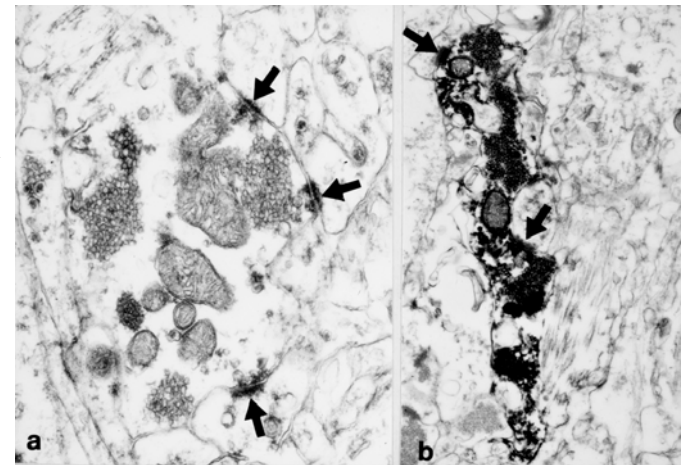


Magloczky et al. Neuroscience 2000, Wittner et al. Neuroscience, 2002

Mossy fiber sprouting – enhanced internal excitatory pathway

The number of granule cell axons terminals increases in the str. moleculare of dentate gyrus and CA3 region. These fibers terminate primarily on principal cells.

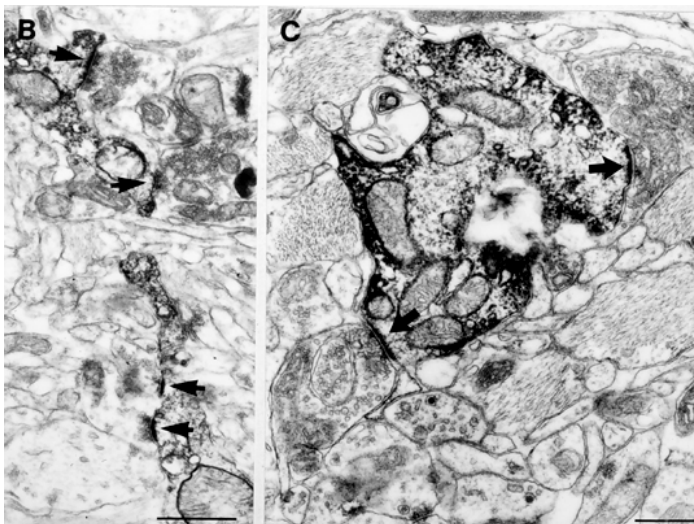
Ann.Neurol., **26** 321-330, *Epilepsia*, **36** 543-558
J Neurosci, **10** 267-82., *J Neurosci*, **13** 1511-22.
Neuroscience, **42** 351-364.



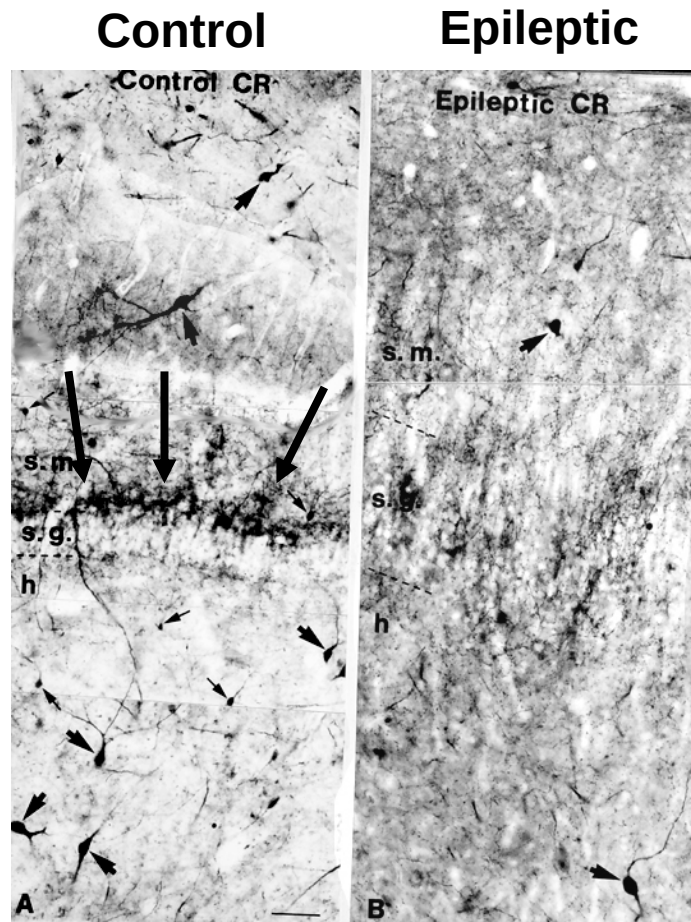
Neuroscience, 1997. **76** 377-85.

Large fraction of the fibers terminates also on dendrites of local interneurons. If the inhibitory cells receive excess stimulation, many of those will die. A subset of these neurons, however will survive and transmit a more effective inhibition.

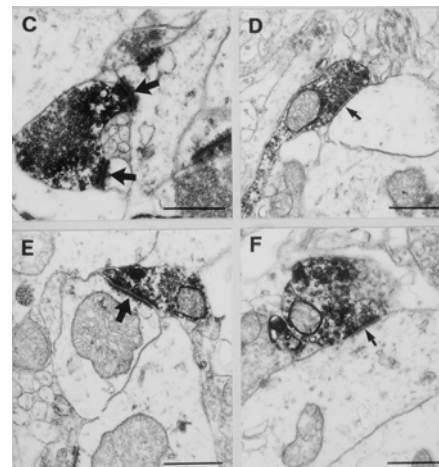
Maglóczy, Neuroscience 2000. 96: 7-25



Sprouting of excitatory input pathways



The supramammillary pathway (SUM) innervates the granule cells of the DG with excitatory terminals, which are arranged in a thin layer in controls (arrows). In contrast, in epileptic patients this layer occupies the whole stratum moleculare, where the axons terminate mainly on granule cells. The SUM contains calretinin. The number of local calretinin-containing inhibitory cells is reduced.



SUM fibers form asymmetric synapses (C,E), whereas the axon terminals of the local interneurons establish symmetric synapses (D,F). Calretinin immunostaining.

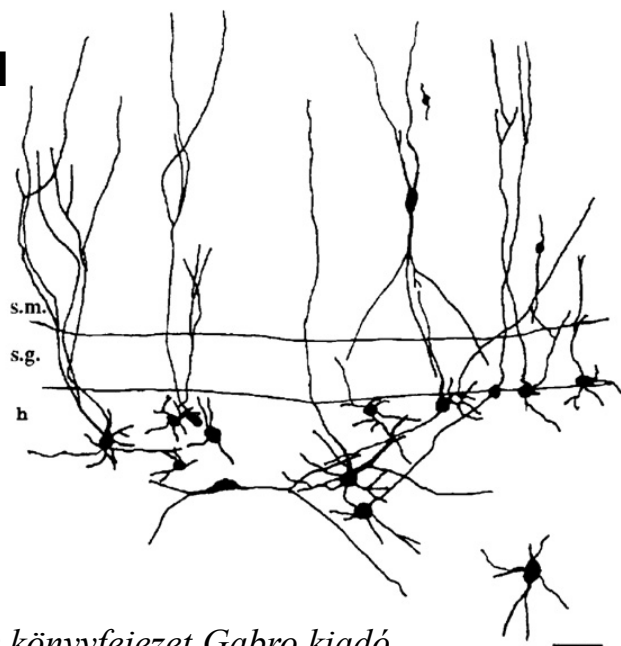
Maglóczy et al
Neuroscience 2000. 96: 7-25

Abnormal localization of interneurons

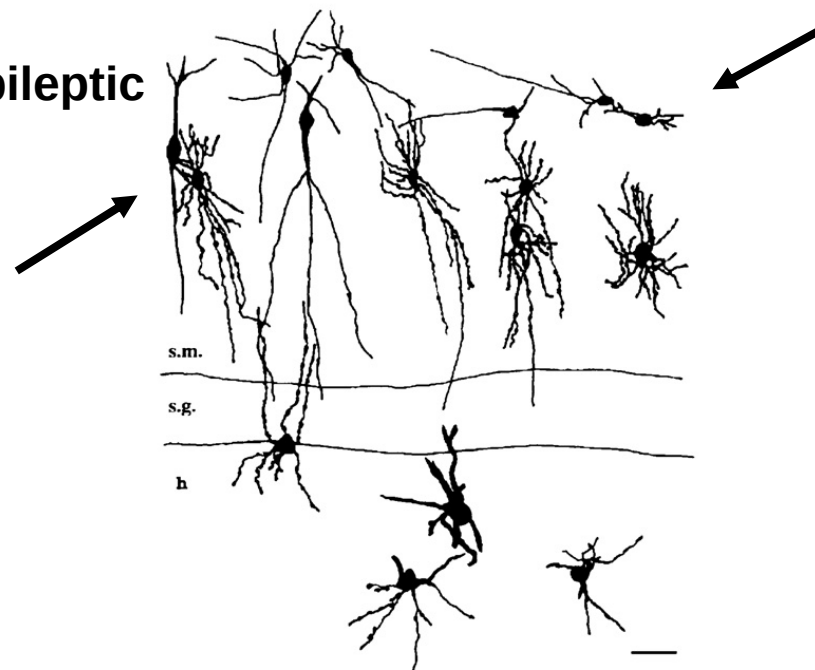
Alterations of input characteristics of the interneurons. Receptor mis-match in the controls. Abnormal localization of interneurons (migration; arrows). Substance

P receptor-immunoreactive inhibitory cells can be detected in the stratum moleculare (sm) of the epileptic hippocampus, in turn, such neurons are localised mainly in the hilus (H) of the control hippocampi. The number of cells are reduced in the hippocampus.

Control

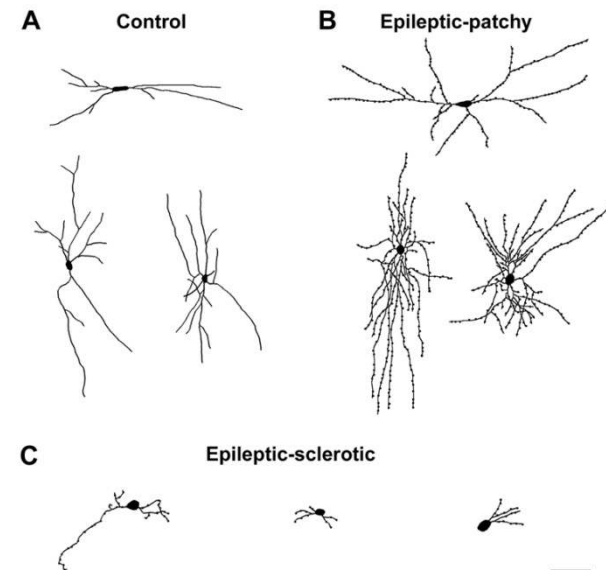
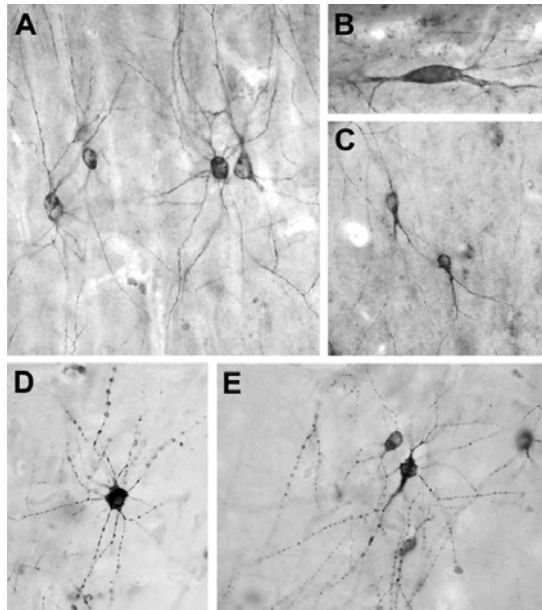


Epileptic



Maglóczy könyvfejezet Gabro kiadó.

Dendritic morphology of Substance P receptor-expressing neurons



Tóth K. et al. 2007
Neuroscience

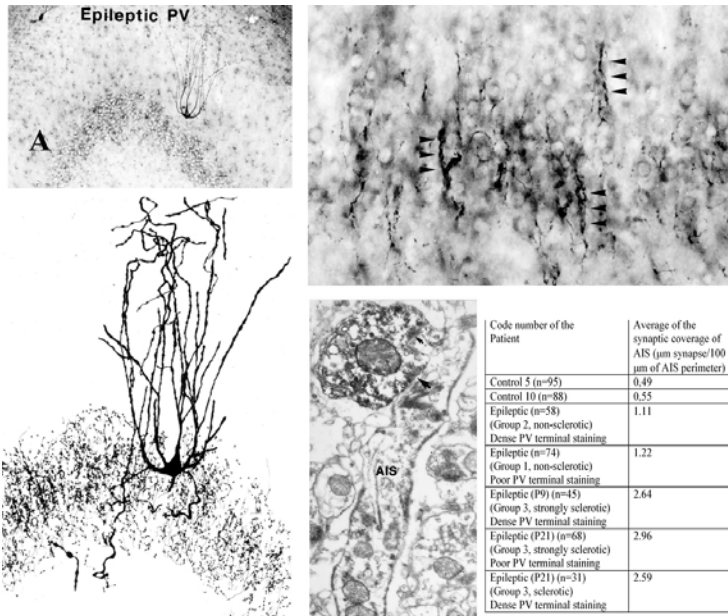
	Number of ramifications/cell (mean stdev)	
Number of cells studied	Stratum oriens	Stratum pyramidale and radiatum
Control (n=33)	4.25 1.04	10.52 3.28
Mild (n=30)	6.63 2.88	11.59 4.62
Patchy, non sclerotic (n=28)	7.25 1.91	21.15 4.68
Sclerotic (n=18)	Stratum oriens, pyramidale and radiatum = 3.22 1.26	

- Changes in the neurochemical markers (e.g. parvalbumin (PV) disappears from the inhibitory cells, number of immunoreactive (IR) cell bodies decreases, but the IR terminals remain visible)
- Axonal sprouting of interneurons. PV-containing axo-axonic cells establish more synapses on the AIS of granule cells of epileptic patients than in controls. Parvalbumin immunostaining.

Axonal sprouting of local interneurons

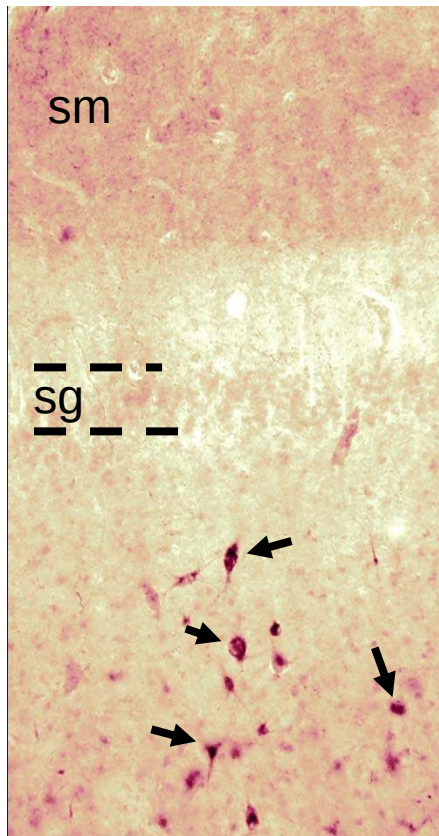
Wittner et al. Neuroscience, 2001

Number of patients (Number of AIS)	Total length of the studied AISs	Synaptic coverage (μm synapse/100 μm AIS)
Control n=10 (n=95)	335.4	0.55
Control n=5 (n=88)	249.3	0.49
Patient n=21 (n=43)	222.7	3.05
Patient n=9 (n=47)	269.8	2.64
Patient n=22 (n=58)	355.33	1.08
Non-sclerotic patient n=15; (n=74)		1.22
Mean of control		0.52
Mean of epileptic patients		1.77

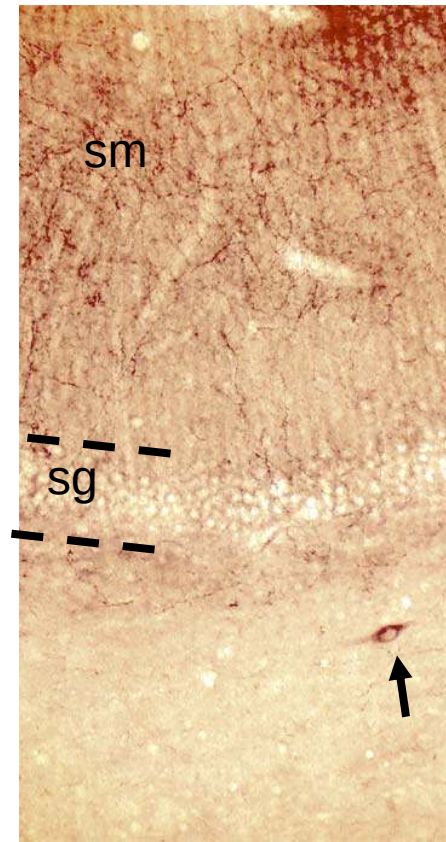


Reduction of the number of local interneurons and their axonal sprouting

Control



Epileptic



- The number of somatostatin-immunoreactive (SOM-IR) cells is reduced, and the SOM-IR axons show sprouting in the dentate gyrus. Somatostatin immunosatining.

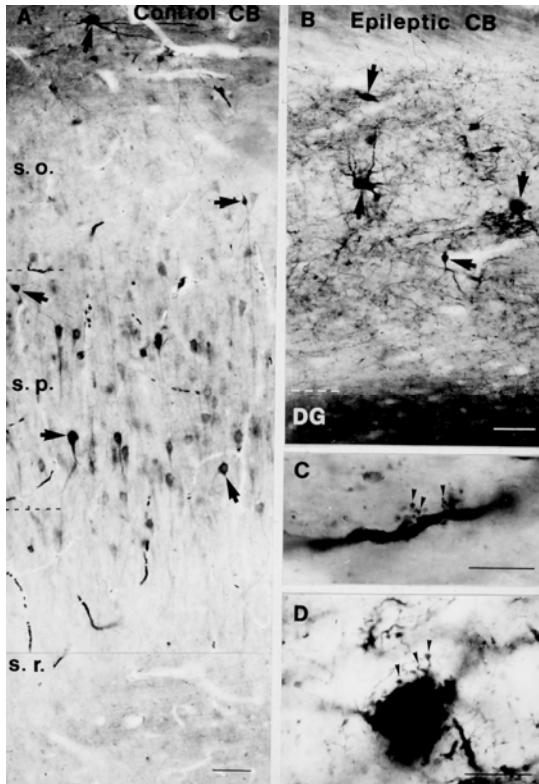
De Lanerolle et al., Brain Res. 495: 387-95

CA1: The morphology of inhibitory cells undergoes changes, the principal cells show functional alterations

Control

Epileptic

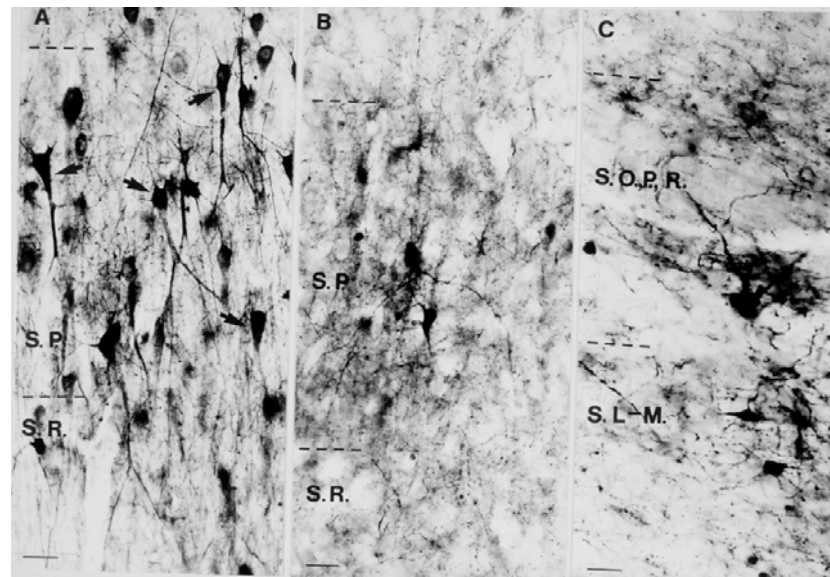
- Changes of neurochemical markers (calbindin disappears from the pyramidal cells in the non sclerotic CA1 region)
- Deformation of interneurons (arrows, dendritic growth, spine formation, hypertrophy)



Control

Non-sclerotic

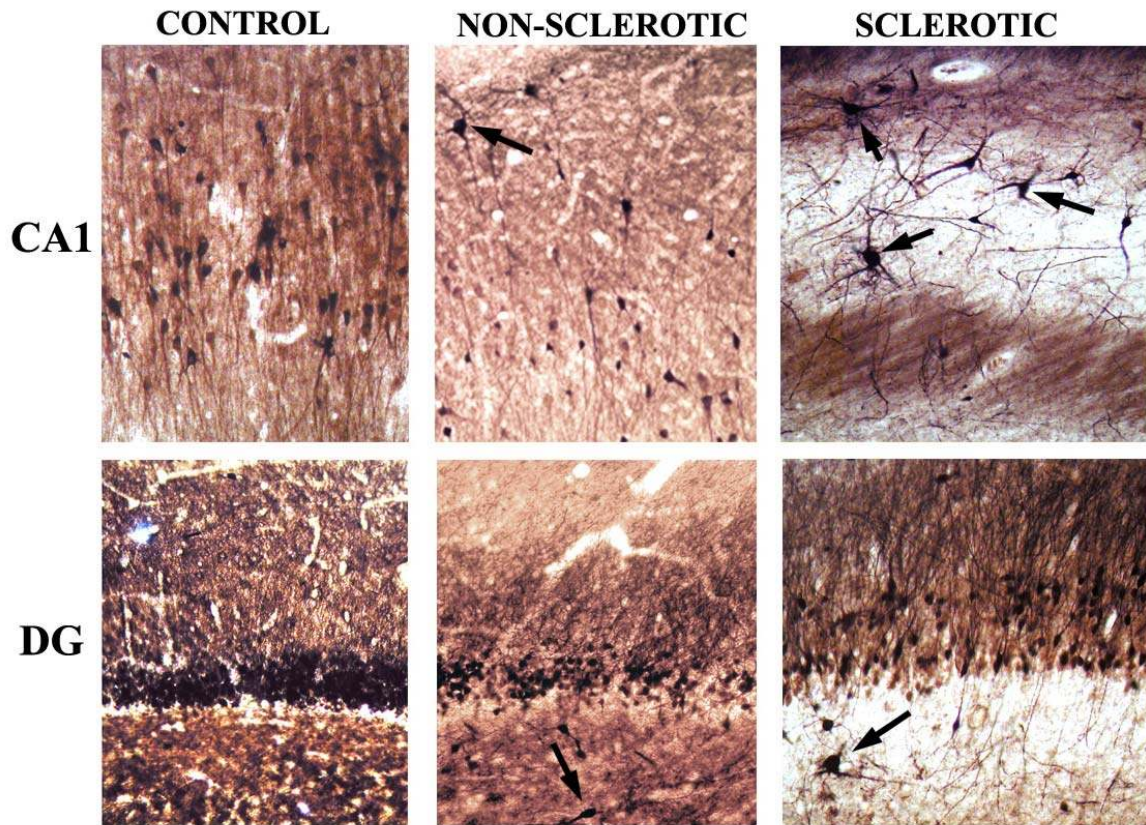
Sclerotic



Calbindin
immunostaining

*Wittner et al.
Neuroscience, 2002*

DG: The morphology of inhibitory cells undergoes changes, the principal cells show functional alterations



- Dispersion of granule cell layer (sg: stratum granulosum)
- Changes of neurochemical markers (calbindin disappears from the granule cells)
- Deformation of interneurons (arrows; dendritic growth, spine formation, hypertrophy)



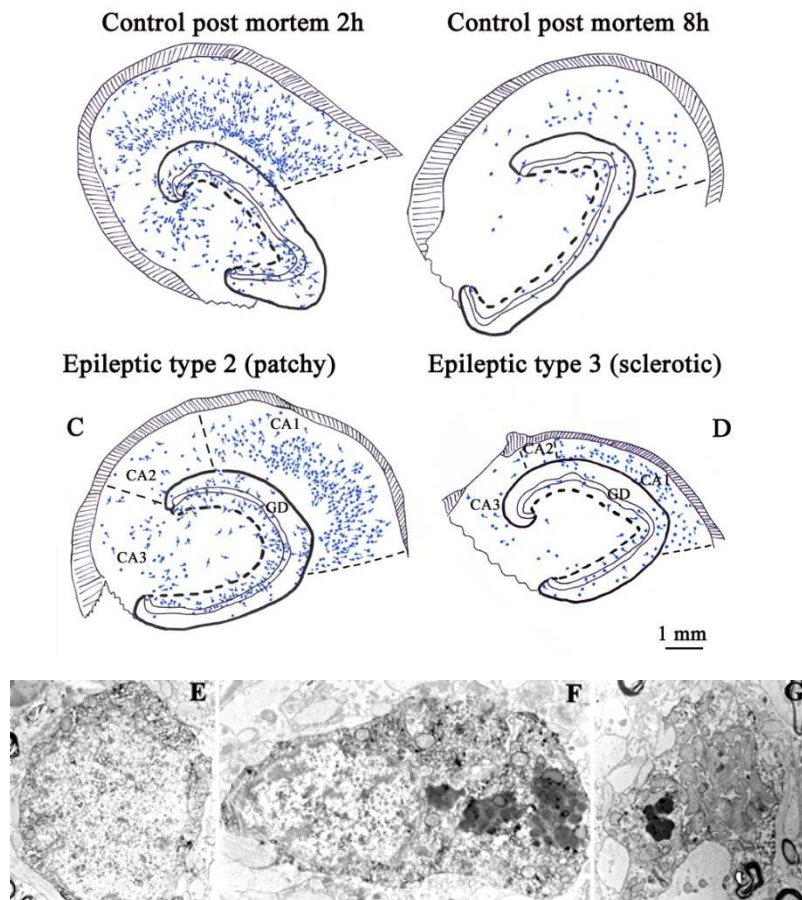
Axonal sprouting of local interneurons

The majority of calbindin-containing inhibitory cells are preserved in the epileptic hippocampus. Contrasting the controls however, they do not project onto principal cells; they rather establish connections with each other resulting in disinhibition.

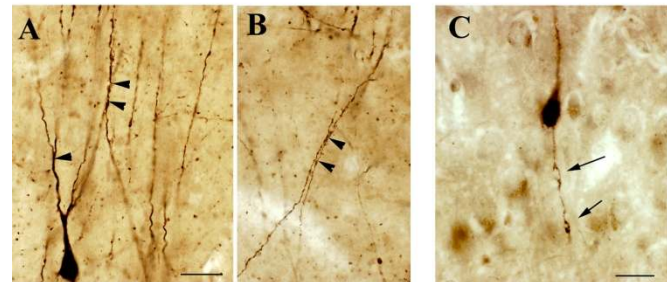
Wittner et al. Neuroscience, 115. 961-978

Group of patients		Examined total perimeter of CB-positive interneuron dendrites (μm)	Total synaptic coverage (μm synapses/ 100 μm dendrite perimeter)	Ratio of asymmetric synaptic length relative to the total synaptic coverage	Ratio of symmetric synaptic length relative to the total synaptic coverage
Control (n=2, C10, 11)	str. or.+pyr.+rad.	489.2	8.63	92.8%	7.2%
	str. lac-mol.	182.3	2.39	86.9%	13.1%
Epileptic non-sclerotic) (n=2, P40, 54)	str. or.+pyr.+rad.	534.7	6.83	75.7%	24.3%
	str. lac-mol.	221.3	2.69	73.2%	26.8%
Epileptic (sclerotic) (n=4, P21, 29, 35, 37)	str. or.+pyr.+rad.	648.7	10.72	69.4%	30.6%
	str. lac-mol.	357.7	4.22	67.0%	33.0%

Loss of interneurons – calretinin-containing cells, human TLE

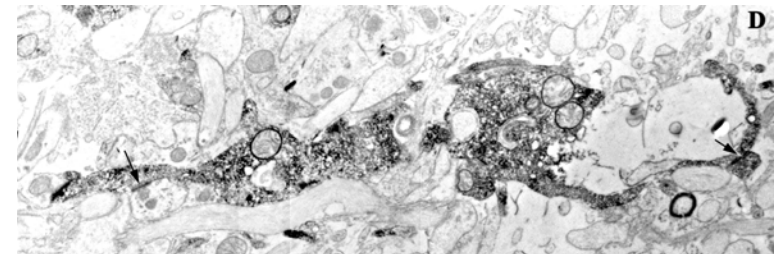
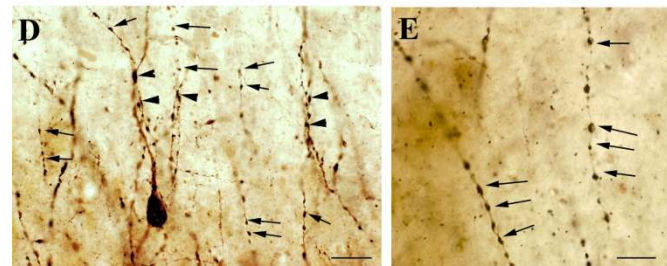


Control (10) post mortem 2h (15) post mortem 8h



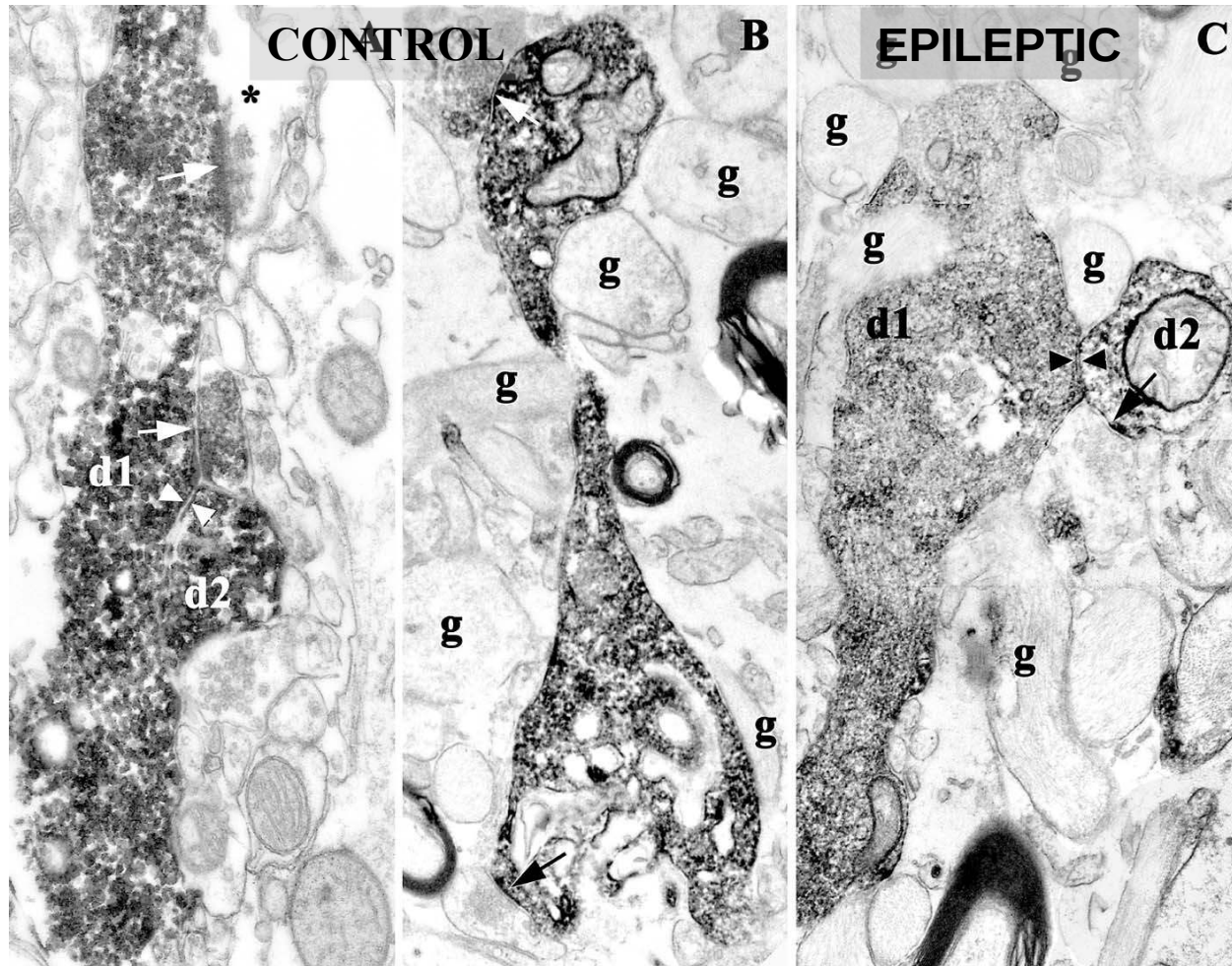
Epileptic “patchy” type

sclerotic type



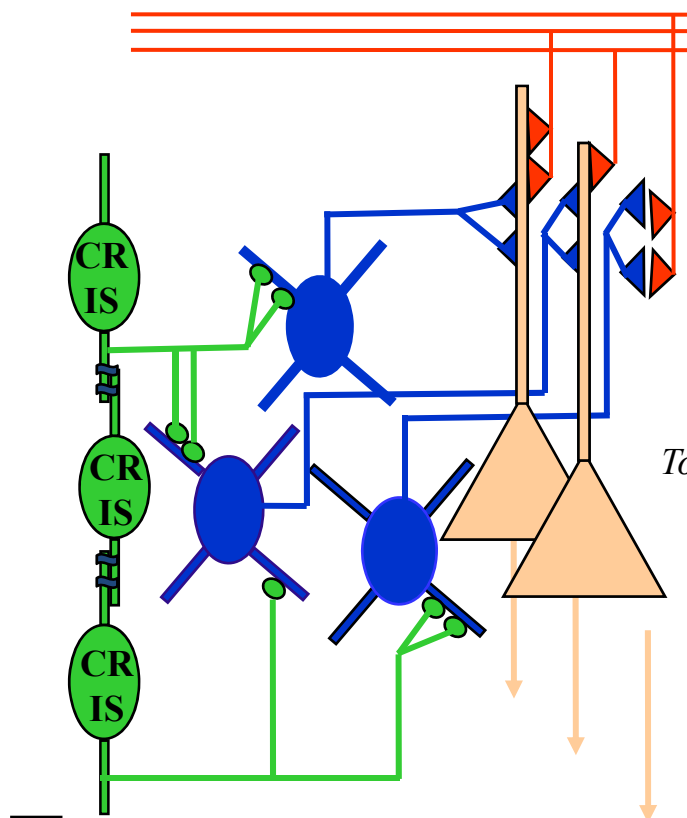
K. Tóth et al. Brain 2010

Calretinin-immunostained dendrites



*Toth K. et al.
Brain 2010*

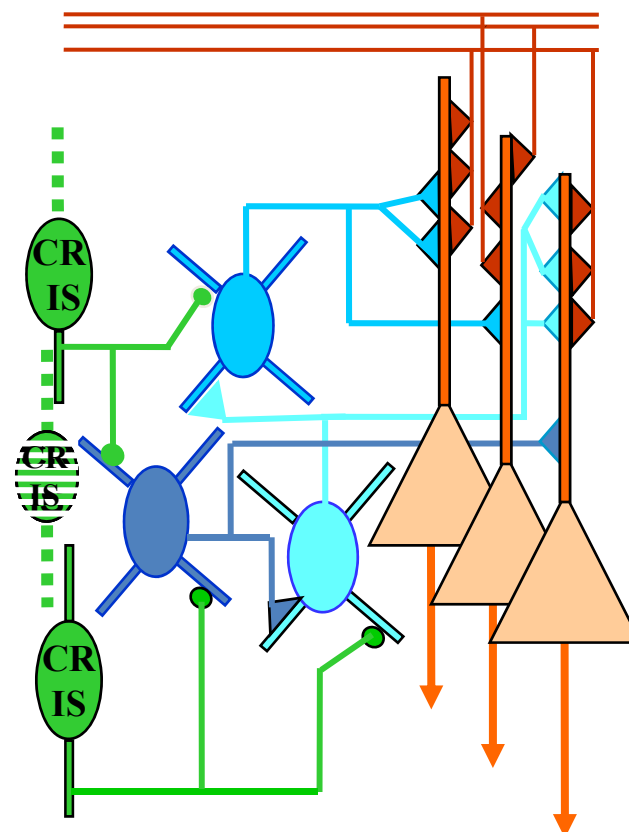
Control



Toth K. Et al. 2010 Brain

-  Interneuron-specific inhibitory cell
-  Synchronized dendritic inhibitory cells
-  Pyramidal cells, no plasticity in dendrites

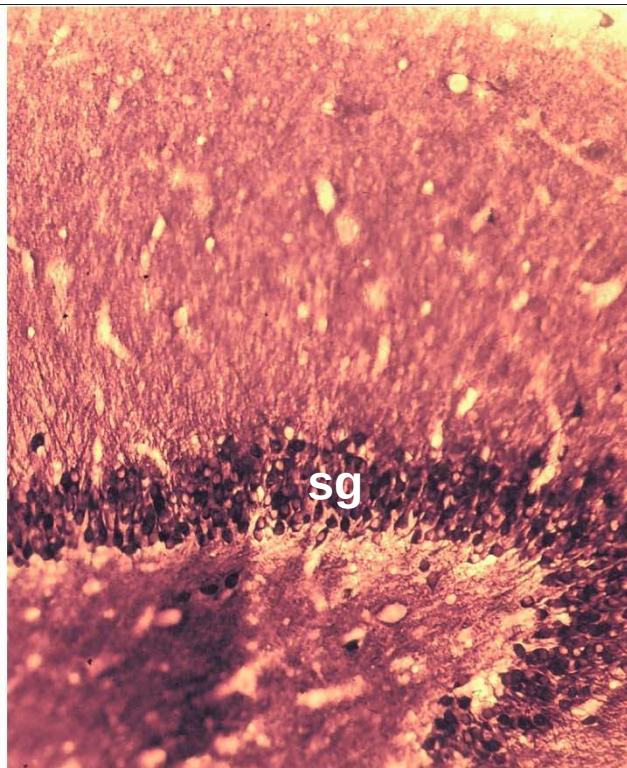
Epileptic



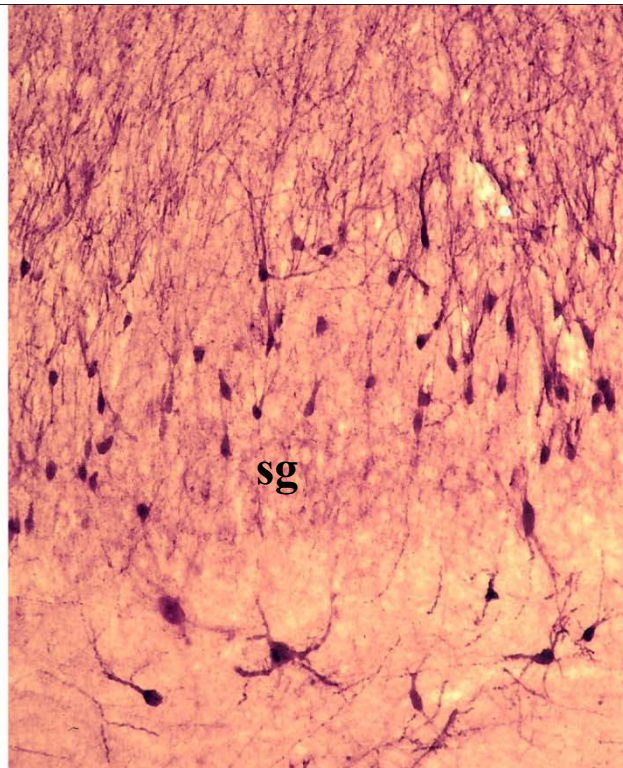
-  Degenerating interneuron-specific inhibitory cell
-  Asynchronous dendritic inhibitory cells
-  Pyramidal dendrites with associative plasticity

DG: The morphology of inhibitory cells undergoes changes, the principal cells show functional alterations

CONTROL



EPILEPTIC



- Dispersion of granule cell layer (sg: stratum granulosum)
- Changes of neurochemical markers (calbindin partially disappears from the granule cells)
- Deformation of interneurons (arrows; dendritic growth, spine formation, hypertrophy)

Functional morphological changes at neuronal network level – the degree of it is in correlation with the loss of principal cells

1. **Cell death:** Pyramidal cells of CA1 and CA3c regions, „sensitive” inhibitory cells (calretinin-, somatostatin-, neuropeptid Y-containing cells supplemented with parvalbumin- and Substance P receptor- containing cells of the CA1 region) and reduction of the number of mossy cells.
2. **Migration of cells:** Dispersion of granule cells, Substance P receptor-expressing inhibitory cells
3. **Deformation of cellular morphology:** Extra dendrites, formation of dendritic- and somatic spines, hypertrophy of cell body (calbindin- and Substance P receptor-containing inhibitory cells)
4. **Neurochemical changes:** Reduction of calbindin-level in the granule cells, and its increase in the interneurons, reduction of parvalbumin-level in the perisomatic inhibitory cells
5. **Axonal sprouting – changes of external and internal neuronal connections**
 - local principal cells: sprouting of mossy fibers and the axons of CA1 pyramidal cells
 - external input pathways: axons within the supramammillary pathway (and the subicular input)
 - local inhibitory interneurons
 - a) enhancement of the perisomatic inhibition in the dentate gyrus
 - b) axonal sprouting of calbindin-containing interneurons in the CA1 region, change in the target cells - dendritic inhibition of CA1 pyramidal cells is replaced with the inhibition of interneurons
6. **Glial fibers -** increased deposition

Changes of neurochemical marker-content

- Calbindin: may disappear from principal cells, but not from interneurons
- Parvalbumin: may disappear from cells, dendrites, sometimes from terminals
- Calretinin: seems to be stably present
- SP: may APPEAR in principal cells
- NPY: stably present in interneurons, mRNA may appear in granule cells. NPY appears in mossy fibres.
- CCK: seems to be stably present

Fate of inhibitory neurons in the epileptic hippocampus

Interneuron types Black: loser Red: winner Green: loser&winner	Non-sclerotic CA1	Sclerotic CA1	Non-sclerotic DG	Sclerotic DG
Parvalbumin/ perisomatic	Survive	Vulnerable	Survive/ sprouting	Survive/ PV disappear, sprouting
Calbindin/ dendritic (CCK)	Survive/ sprouting	Subset of them survive/dendritic growth, spine formation, sprouting	Survive	Survive/ growth
SPR/ dendritic	Survive/ dendritic growing	Vulnerable	Survive	Survive/ migration, dendritic growth
Calretinin/ dendritic + interneuron specific	Survive/ dendritic degeneration	Vulnerable	Survive/ dendritic degeneration	Subset of them vulnerable

Epilepsy and the inhibitory neuronal network

EPILEPTIC REORGANISATION =

Cell death + sprouting: changes of the cellular connections and excitability

Loss of interneuron specific inhibitory cells results in a **reduction of the effectiveness of dendritic inhibition.**

Reduction of the dendritic inhibition and the sprouting of excitatory pathways result in an **abnormal potentiation of the excitatory input.**

The increased **perisomatic inhibition may increase the probability of synchronised cellular activity.** The neuronal network becomes destabilised and consequently seizures develop more easily.

Cellular death is induced by the increase of **calcium levels deriving from the extracellular space**, threshold phenomena. Loss of interneurons in the CA1 may depend on the survival of target cells.

Epileptic reorganisation

Cell death + alterations in the neuronal connectivity and excitability

1. **Reduction of dendritic inhibition.** ↓
2. **Reduction of interneuron-specific inhibition.** ↓
3. **Increase of excitatory input onto dendrites** ↑
4. **Increase of perisomatic inhibition** ↑

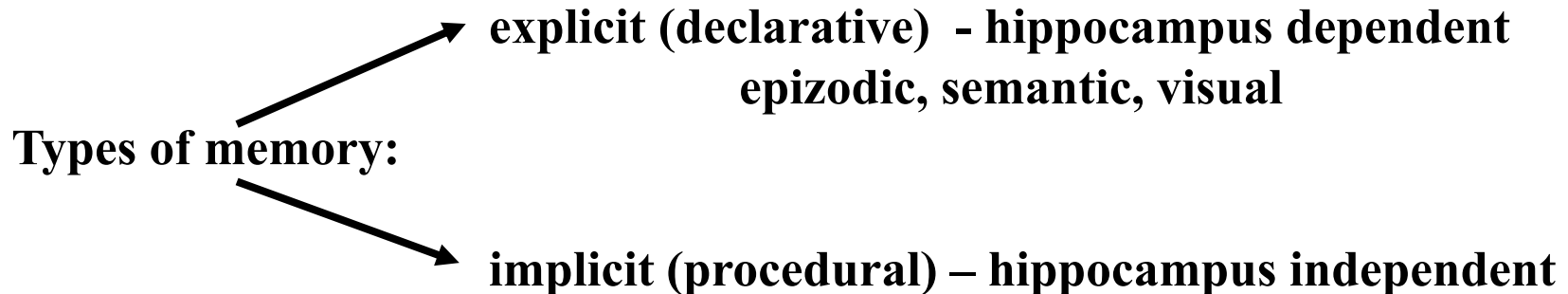
The neuronal network becomes destabilised, synchronisation is increased within. Seizures develop more easily.

1. Loss of inhibitory neurons develops in all types of epilepsy, independent of the sclerosis.
2. Axon sprouting (excitatory and inhibitory) develops in all types of epilepsy, independent of the sclerosis.
3. Loss of principal cells is likely to depend on the extent of excitation, threshold phenomena.

EPILEPSY = SCLEROSIS and DUAL PATHOLOGY - other regions are also reorganised!

Function of hippocampus (+ limbic system)

- **memory (transition of short-term and long-term)**
- **learning**
- **spatial orientation**
- **emotional background of events, behavioral regulation**



Szirmai: Neurológia

Participation of the left and right hippocampus in memory processing

DOMINANT

(left, by right-handed people)

speech recognition
word recognition
memorising words
echoing words
object of tales

SUBDOMINANT (right)

visual capabilities
face recognition
spatial rotation of images
details of tales

Experimental epilepsy models (according to the triggering methods)

- Genetic modifications
- Kindling (repeated small electric or chemical stimulation, till the level of spontaneously recurrent seizures)
- Seizure induced by electric stimulation
- Application of excitatory amino acid analogues
- Alteration of the levels of inhibitory-excitatory amino acids
- Alteration of the operation of ion channels
- Alteration of the kationic concentrations etc.

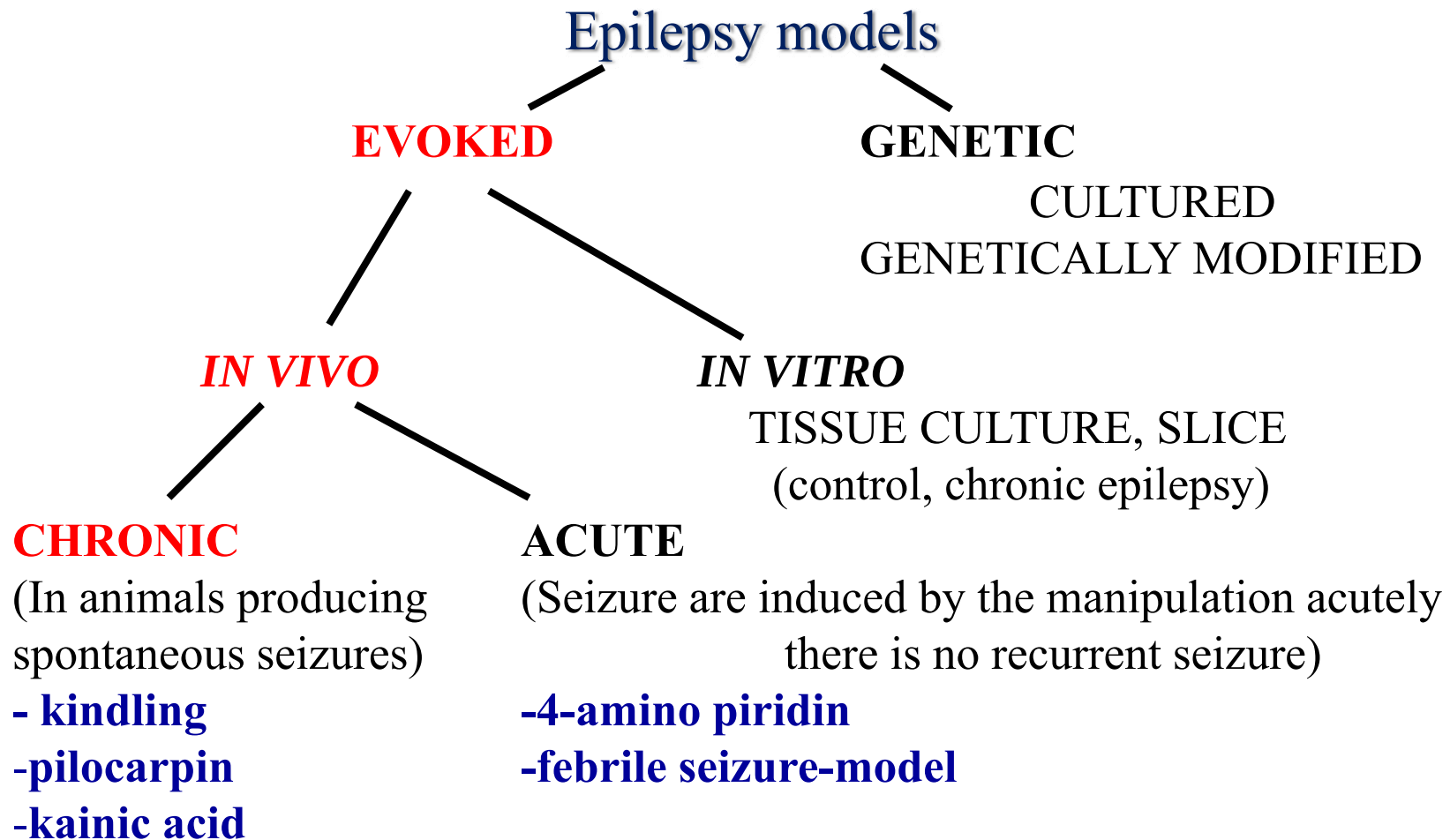
Experimental epilepsy models (according to the phenotype)

1. **Acute seizure model** (slice, cell culture)

Tissue is sampled from control animal, and the seizure is triggered with a chemical agent. Epileptogenesis is studied, i.e. behavior of single cells in response to a seizure. There is no network effect and reorganisation. This is the model of synchronous activity.

2. **Chronic epilepsy model**

It is studied in animals producing spontaneous seizures (such animals are produced by application of pilocarpine, kindling, or kainic acid). There is reorganization. The effect of long-term rearrangement and the network changes can be studied in this model.



Experimental models of Temporal Lobe Epilepsy

Kindling model

- It provides a model only for seizure, there is no/a few/ cell death
- There is sprouting of mossy fibers, level of calbindin is reduced
- It is a partial seizure model

Pilocarpine (non-specific muscarinic-receptor agonist) model

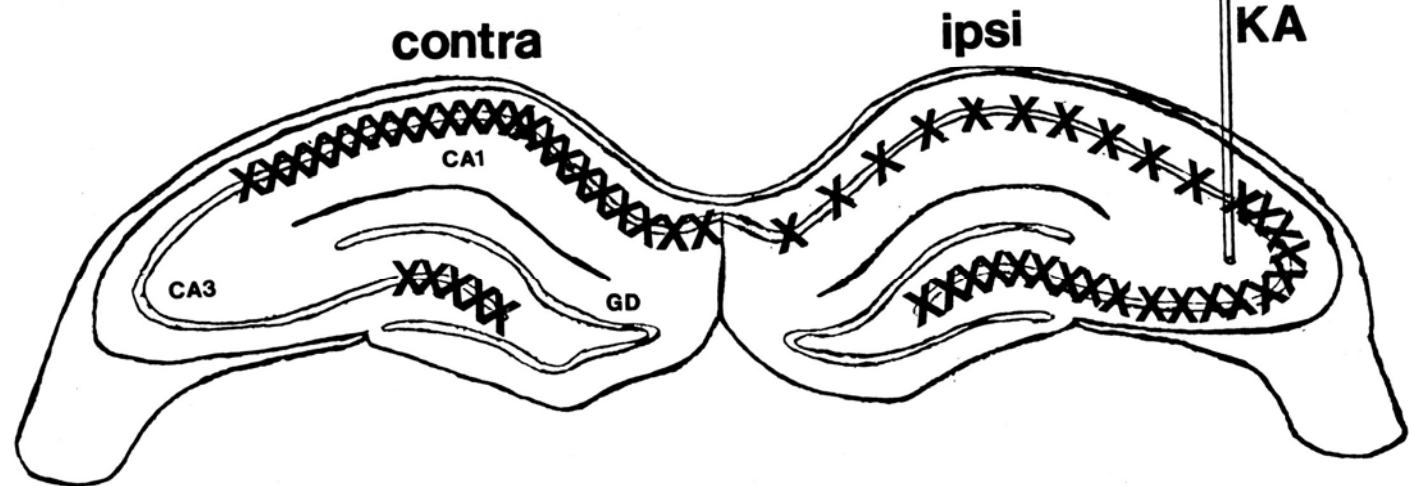
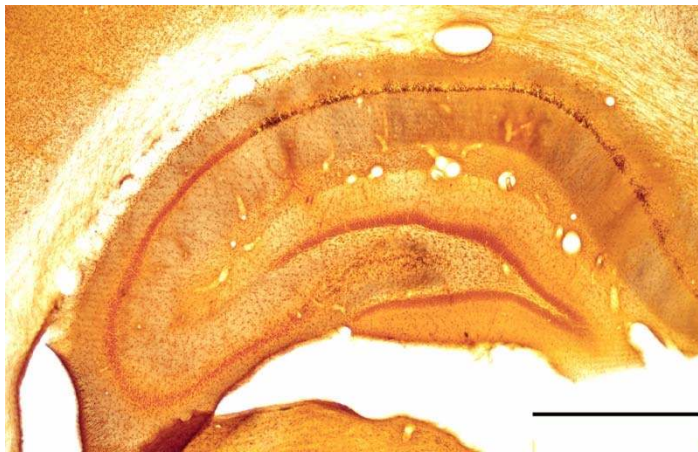
- Administration of 300-380 mg/kg pilocarpine i.p. (+scopolamine to reduce peripheral cholinergic effects)
- Acute effect is status epilepticus (24 h)
then a latent period (days-week)
- Chronically recurrent seizures
- Cell death characteristic for TLE is in the hippocampus

Experimental models of Temporal Lobe Epilepsy

Kainic acid (glutamate analogue, effects through kainate receptors) model

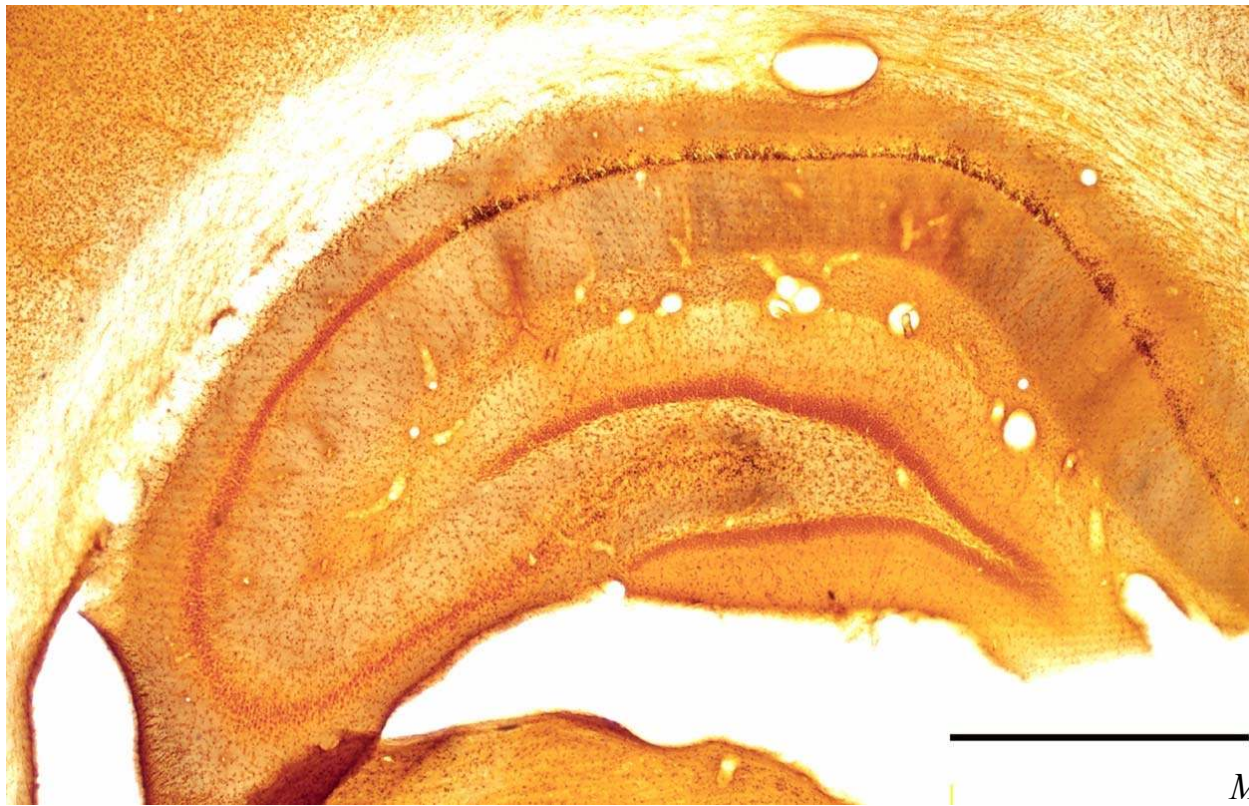
- Highest density of receptor of the drug on the pyramidal cells of CA3 region and the mossy fibers
- direct effect through its specific receptors
- it spares the axons, indirect effects through axonal pathways
- can be administered: intraperitoneally, subcutaneously, intracerebroventricularly, intracerebrally
- resultant cell death varies, seizures are always similar to the one characterises the TLE, status epilepticus appears if it applied in large dose. It is suitable also for chemical kindling.
- ipsilateral kainate injection in the hippocampus/entorhinal cortex results in cell death in the contralateral hippocampus, the appearance of which is very similar to the one observed in the hippocampus of TLE patients.

Kainate model, ipsilateral kainate injection into the CA3 region



*Magloczky and Freund,
Neuroscience 1993.*

Cell death in the contralateral hippocampus after ipsilateral kainate injection: Loss of CA3 and CA1 pyramidal cells shows similar histology to the one observed in human hippocampal sclerosis.

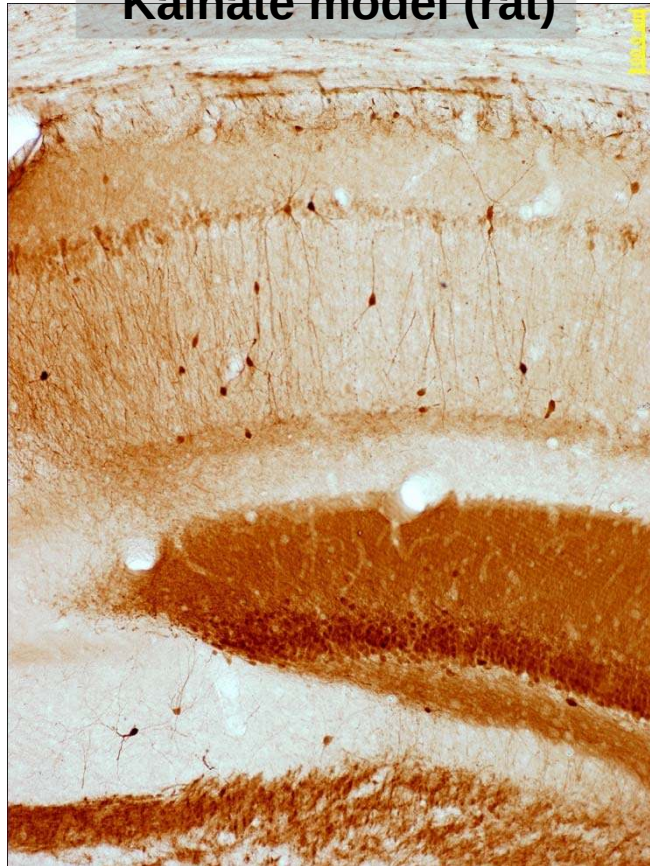


Gallyas silver
impregnation.

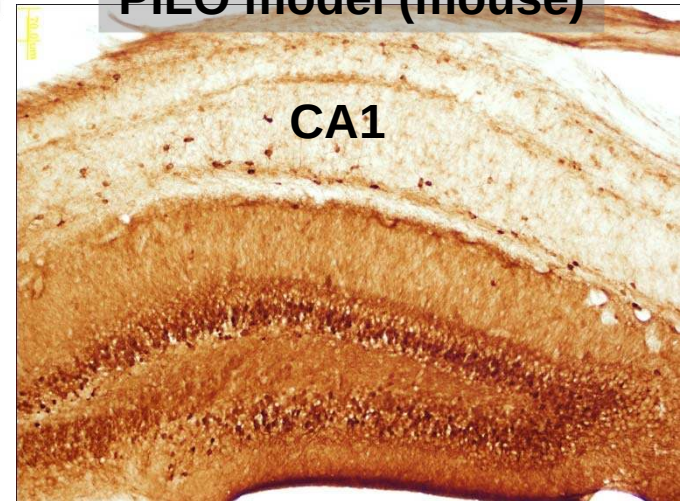
Magloczky et al. Neuroscience 1993.

Calbindin-immunoreactive cells in two models of epilepsy

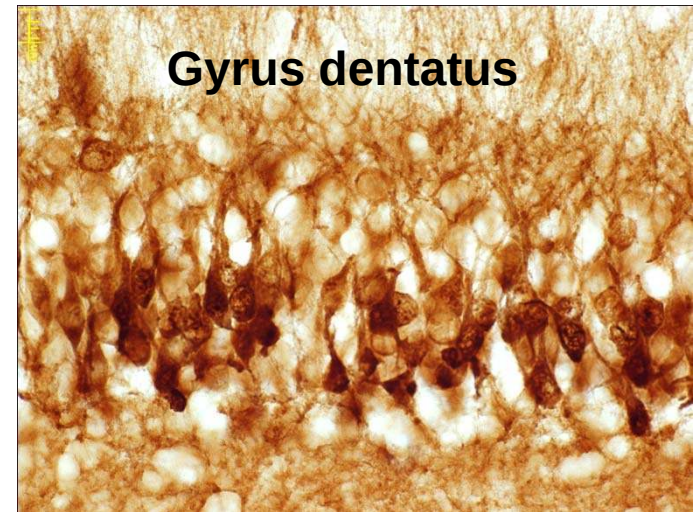
Kainate model (rat)



PILO model (mouse)

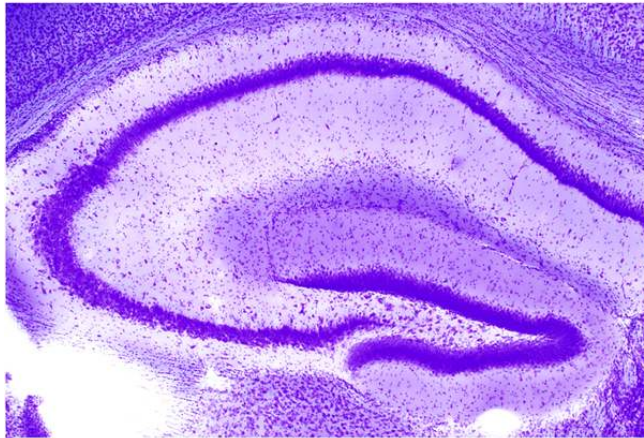


Gyrus dentatus

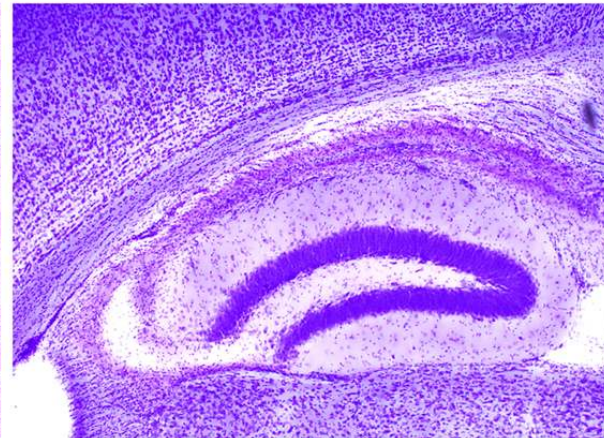


Two types of cell loss in pilocarpine-induced epilepsy (weak-strong SE)

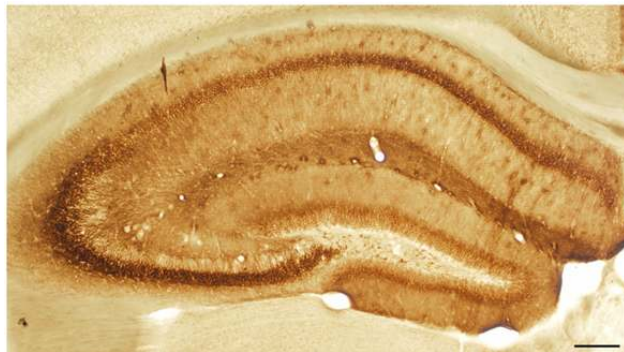
Pilo EPI weak



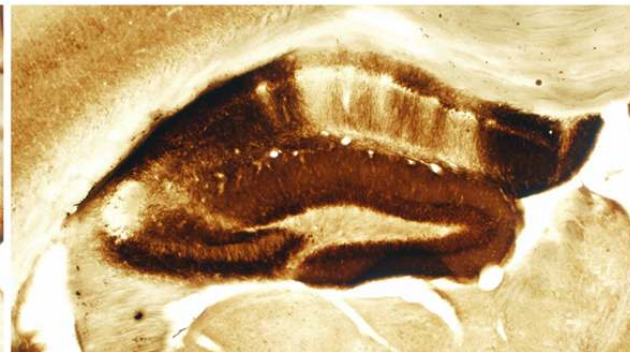
Pilo Epi strong



Pilo EPI weak GluR 2/3



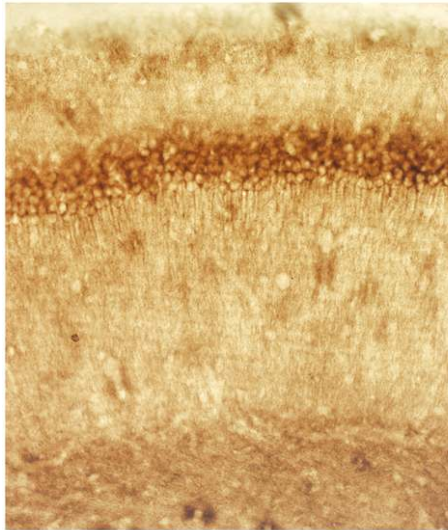
Pilo EPI strong GluR 2/3



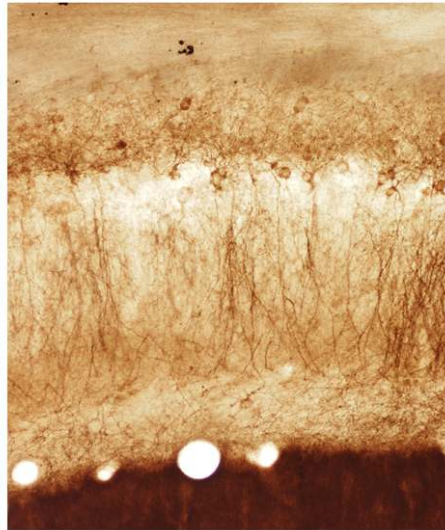
Two types of cell loss in pilocarpine-induced epilepsy (weak-strong SE)

CA1

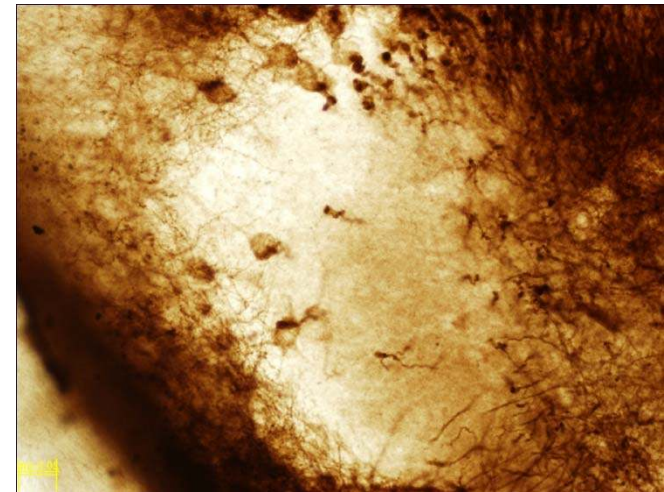
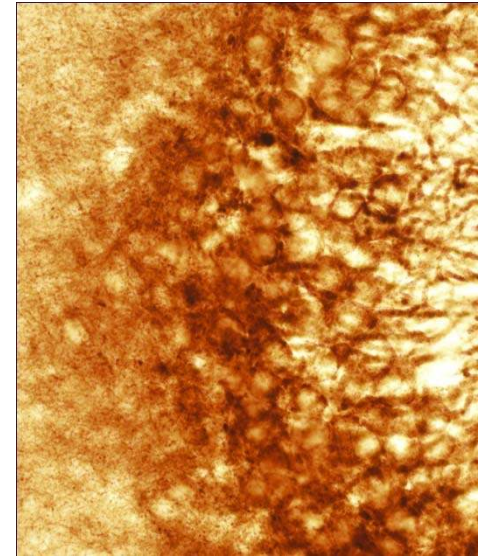
Pilo EPI weak GluR2/3



Pilo EPI strong GluR2/3

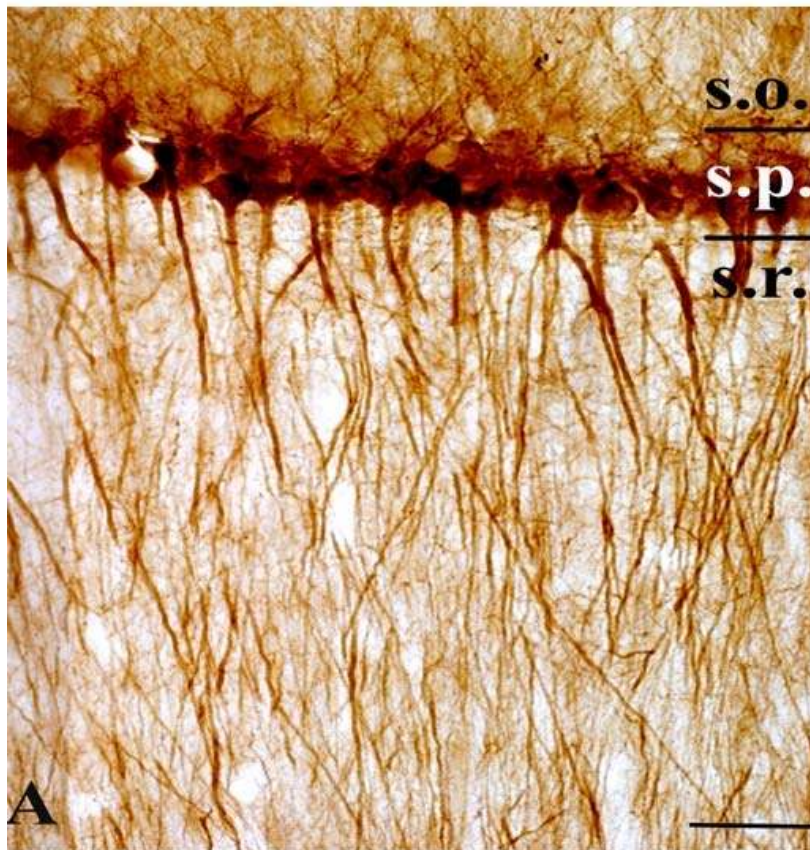


CA3

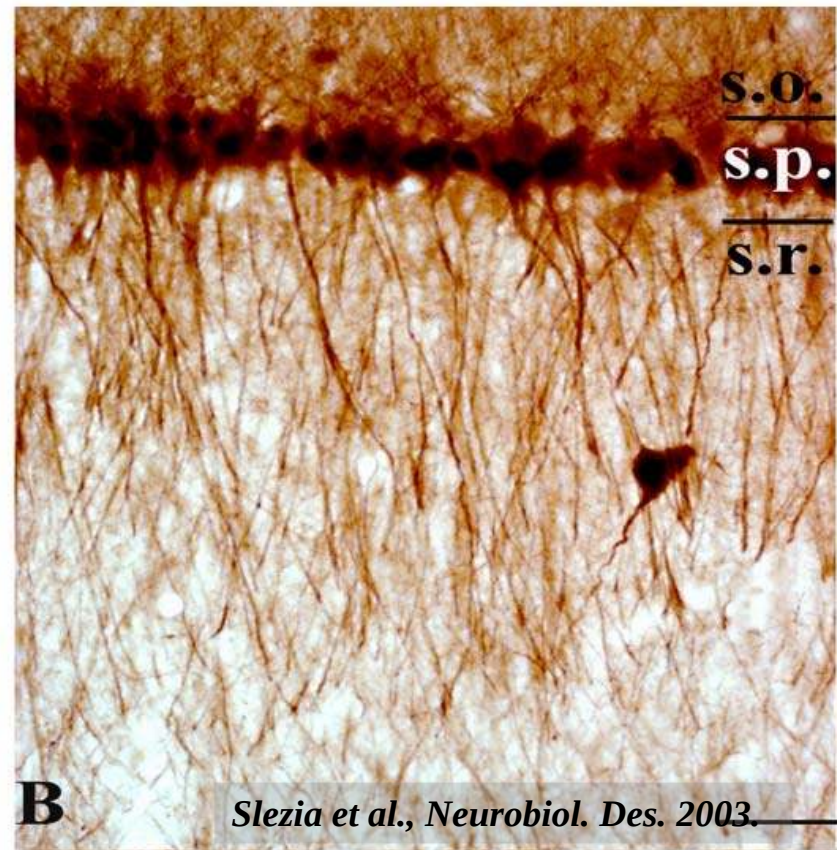


AP model, calbindin-containing cells in the CA1 region

Control

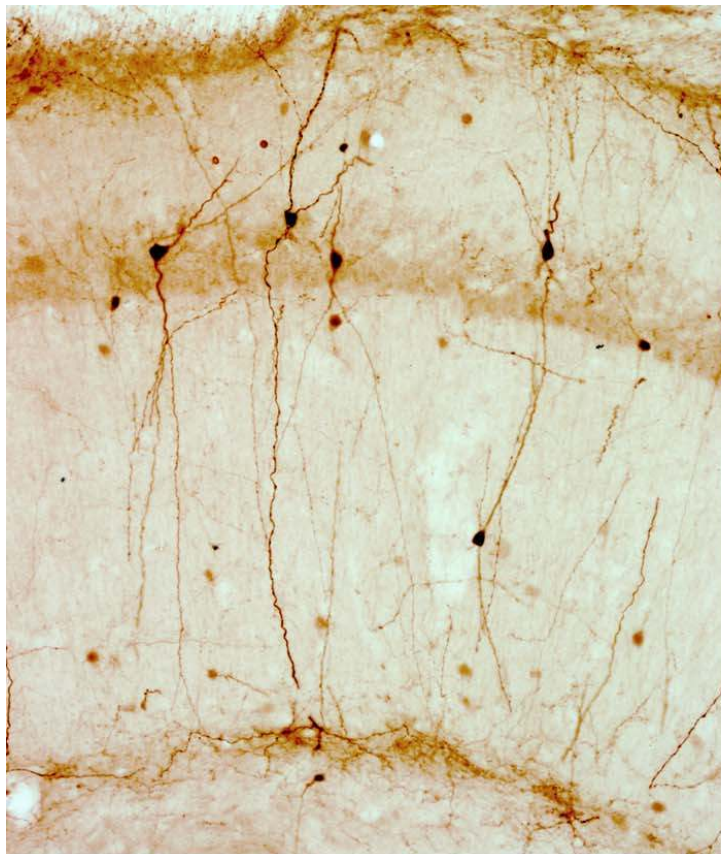


3-AP-treated



Kainate model, calretinin-containing cells, CA1, rat

Control

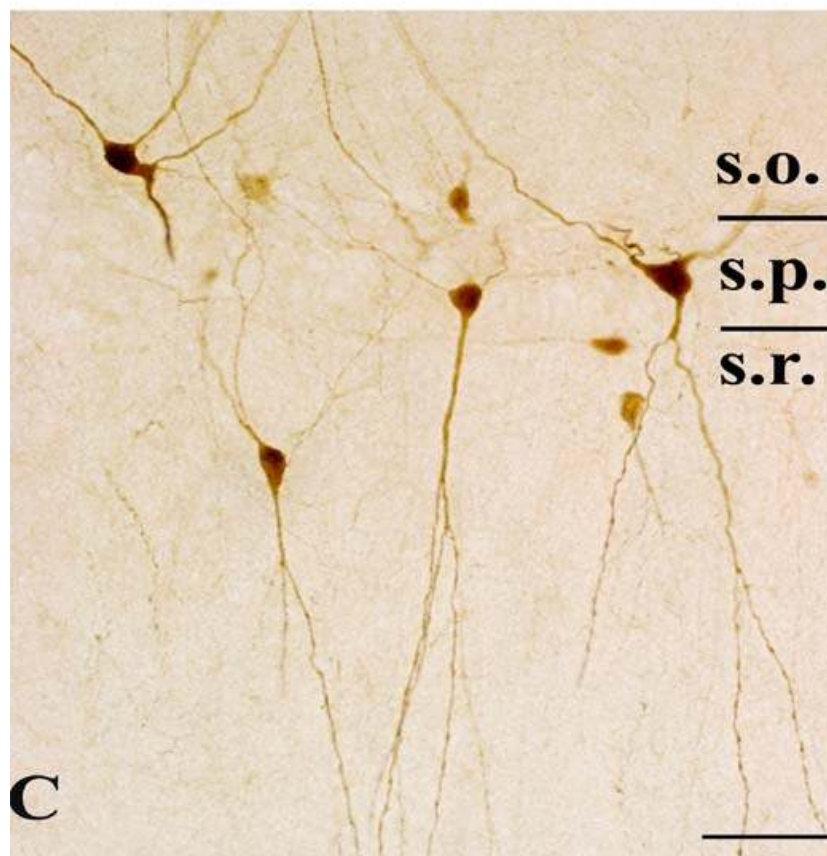


Epileptic



4-AP model, calretinin-containing cells in the rat CA1 region

Control



4-AP-treated



Classification of TLE patients according to the extent of cell death (n=50)

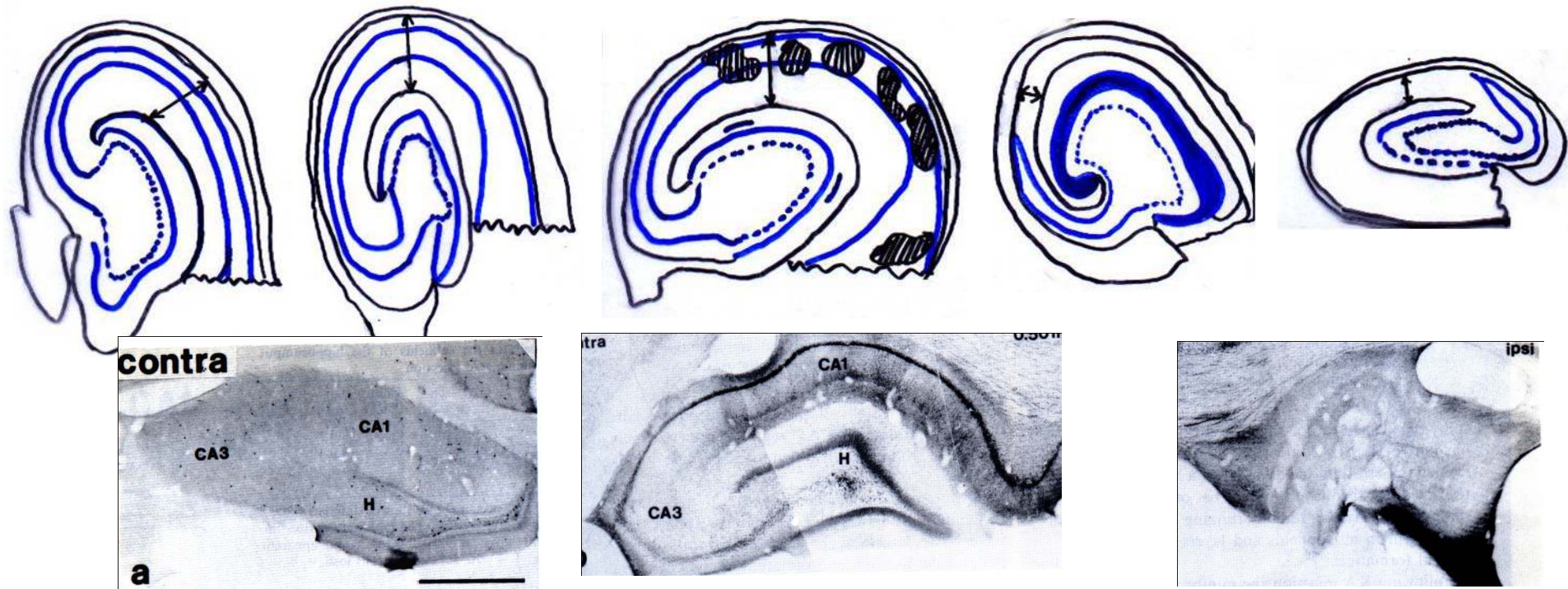
Control

1. non-sclerotic

2. non-sclerotic

3. sclerotic

4. gliotic



1: Kindling, low dose kainate
4-AP injection

3: Unilateral, medium dose kainate,
Contralateral hc., pilocarpine

4: Icv, intrahippocampal or systemic
injection of large dose kainate

Drawing of Escher may also demonstrate the relationship between the epileptic reorganization and the epileptic seizures

