Basics in epileptogenesis

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강의 내용

- Ictogenesis
- Basic concepts on epileptogenesis (continuous progression)
- Axonal sprouting, Astrocytosis
- Ectopic neurogenesis
- Inflammation – curved by celecoxib, EPO
- Febrile seizures & Cortical dysplasia
- Hippocampal sclerosis (Dual hit model)
- MDR epilepsy: p-gp and microRNA changes

Seizure

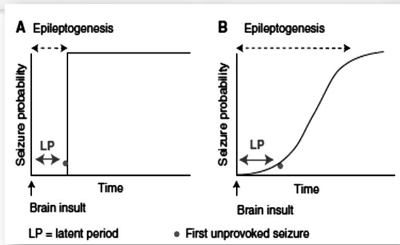
- Electrophysiologic phenomenon
- Pyramidal neuron
- Hyperexcitability
- Network Hypersynchrony
- Tsunami
- Spontaneous Remission (30sec – 1 min)
- Ionic Imbalance around neuronal membrane

Basic concepts on epileptogenesis

- "Epileptogenesis is the process by which a brain network that was previously normal is functionally altered toward increased seizure susceptibility, thus having an enhanced probability to generate spontaneous recurrent seizures"
- Epileptogenesis refers to the development and extension of tissue capable of generating SRSs, resulting in (1) development of an epileptic condition, and/or (2) progression of the epilepsy after it is established.

Pitkanen A, 2015, Cold Spring Harbor Perspectives in Medicine

Epileptogenesis 개념의 변화



The major difference to the previous concept is that the term "epileptogenesis" no longer refers only to the time period between the epileptogenic insult and diagnosis of epilepsy (Fig. 1A);

rather, the term epileptogenesis now includes the mechanisms of progression that can continue to occur even after the diagnosis of epilepsy (Fig. 1B).

Pitkanen A, 2015, Cold Spring Harbor Perspectives in Medicine

Genes/CD

Prolonged Febrile seizures

Astrocyte Death

Hypertrophy and Genesis of Astrocyte

Inflammation
mTOR activation
BBB disruption

LATENT PERIOD

Axonal sprouting
Subclinical seizures
Ongoing Neuronal Death
Loss of Astrocytic 3D domain
Extensive Epigenetic Changes

Emergence of Clinical Epilepsy

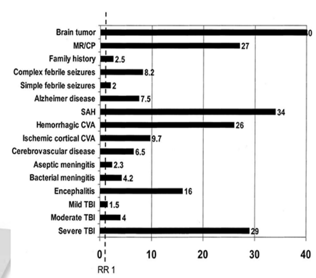
Frequent Hyperexcitability
Hypersynchrony
Ectopic Granule Cells
Angiogenesis
Acquired channelopathy

Multidrug Resistant Epilepsy

Hippocampal Sclerosis
Increased drug efflux pump
Reactive Gliosis
Cortical Dysplasia

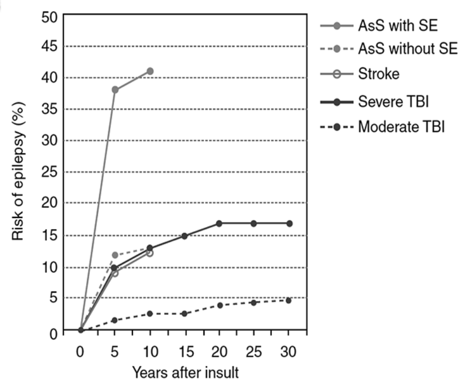
Initiating events

Latent period



- Delay from a specific insult to the occurrence of seizures.
  - Febrile seizures -> TLE (7.5 yrs)
  - Severe TBI -> epilepsy (high risk more than 10 years)
- "Therapeutic Window" for antiepileptogenesis

Rapid epileptogenesis after status epilepticus



Pitkanen A, 2015, Cold Spring Harbor Perspectives in Medicine

	Association with post-stroke epileptogenesis
Life-style factors	
Smoking[30,66]	No
Alcohol use*[30,73,35,66]	Yes/no
Acute metabolic disturbances	
Acid–base imbalance[66]	No
Electrolyte imbalance[35,66]	No
Hyperglycaemia*[73,35]	Yes
Non-CNS morbidities	
Diabetes 1 or 2*[11,35,66]	Yes/no
Dyslipidaemia[66]	No
Renal insufficiency[35,66]	No
Hypertension[35,66,62,68]	Yes/no
Coronary heart disease or myocardial infarction*[11,35,66]	Yes/no
Peripheral infections*[73,66]	Yes/no
CNS morbidities	
Early seizures*[71,73,33,69]	Yes
Status epilepticus within 2 weeks post stroke[70]	No
Depression or use of antidepressants*[73,66]	Yes
Dementia[71]	Yes
Pharmacotherapy	
Antiepileptic drugs[72]	No
α1-noradrenergic blockers[72]	No
α2-noradrenergic agonists[72]	No
benzodiazepines[72]	No
α2δ voltage-sensitive calcium-channel blockers[72]	No
Statins*[73]	Yes

*Because data derived from ischaemic stroke only are meagre, cohorts reported in studies shown also include other stroke types.

Table 3: Peri-injury exposome and risk of epileptogenesis after cerebral stroke

Panel: **Caveats to the interpretation of clinical data related to post-stroke epileptogenesis**

Accuracy of stroke diagnosis

Prevalence of different types of stroke in a given study population

Definitions of early and late seizures and epilepsy

Follow-up duration

Sample size

Heterogeneity in study designs

Use of univariate versus multivariate statistics for data analysis

Availability and analysis of CT and MRI scans for diagnosis and follow-up

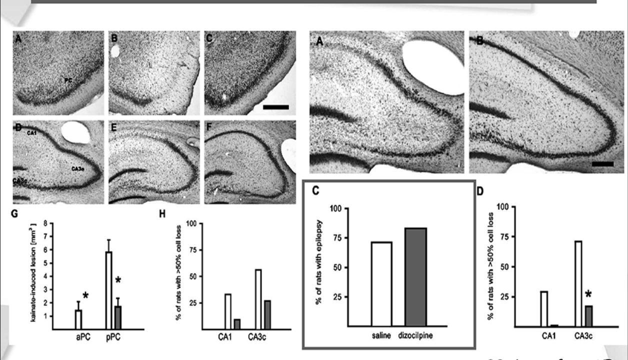
Accuracy regarding the location and type of primary lesion

Availability of EEG for detection of epileptiform activity (seizures and status epilepticus)

Use of antiepileptic drugs or other medications acutely or during follow-up

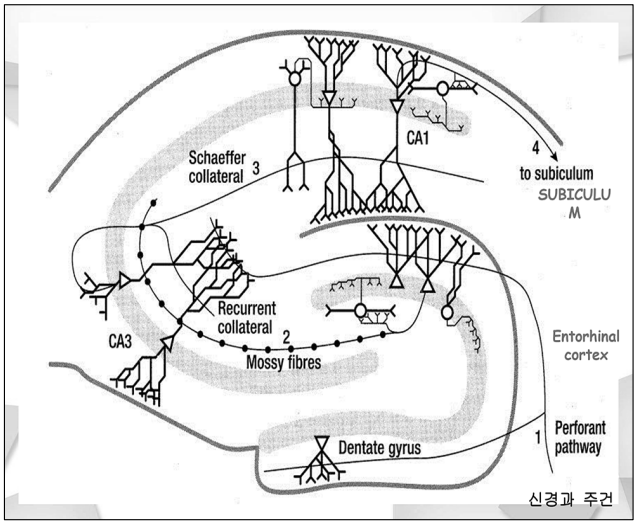
Pitkanen A, 2015, Lancet Neurol

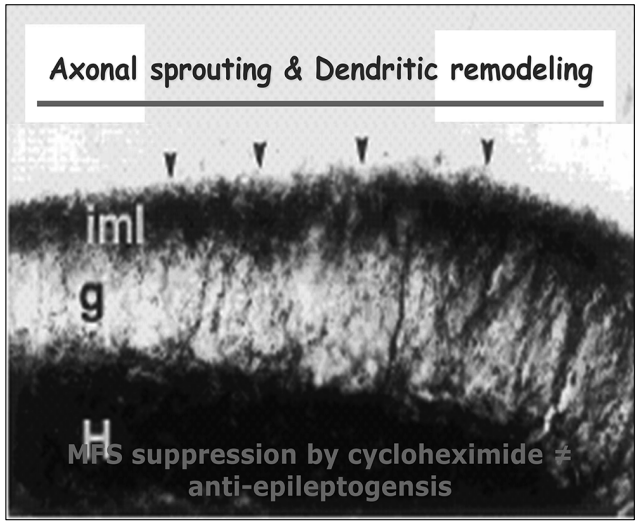
발작에 의한 세포손상을 막아도 일은 진행된다.



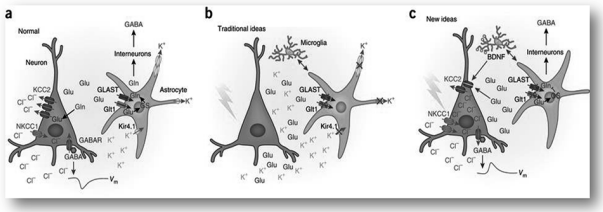
3 days after SE

28 days after SE



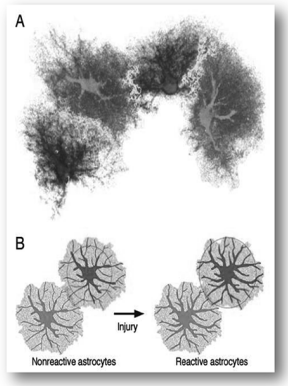


Astrocytes are active modulators of neuronal activity

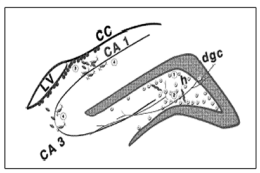


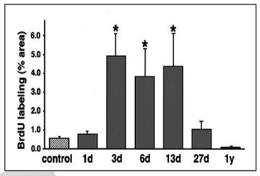
- Traditional: Kir4.1, Glt1, GLAST, AQP4, Connexin 30, 43
- New concepts
  1. KCC2 (CCC): downregulated
  2. NKCC1 (CCC): upregulated
  3. GS: downregulated, reduction of GABAergic inhibition
  4. ECM remodeling
  5. GAT (GABA reuptake): tiagabine

Epileptic Cortex에서는 Astrocyte들이 각자의 3차원 도메인을 잃어버리고, 영역이 겹치게 되어 신호전달의 손상이 생긴다.

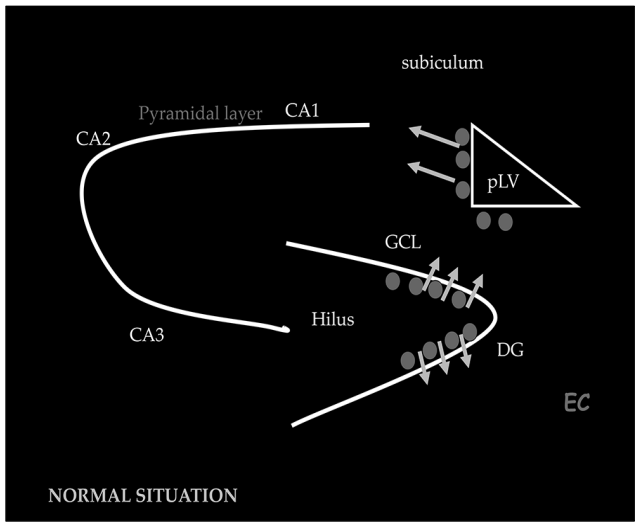


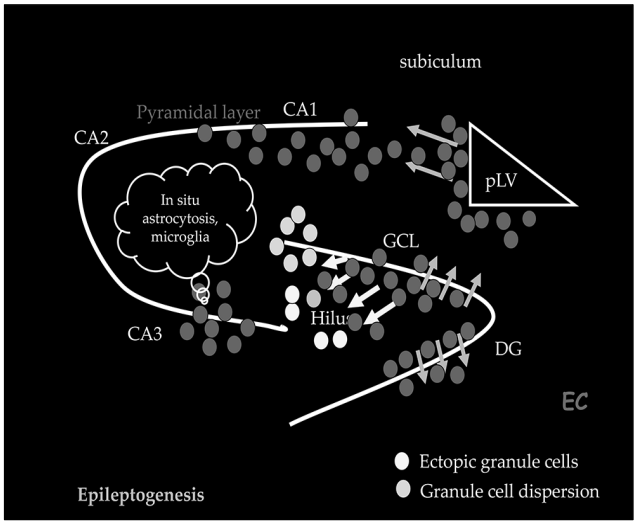
Seizure-associated Cell proliferation in Hippocampus





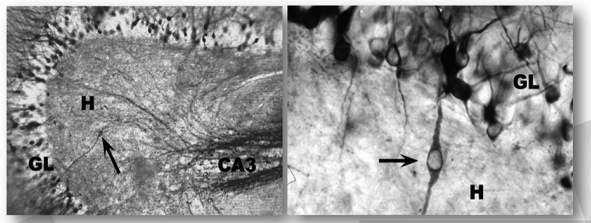
- Enhanced by
  - Electrical stimulation
  - Glutamate
  - Injury-associated mediator (Lipid mediators, e.g. PGE2)
- SGL and SVZ
- 3 days - 2 weeks



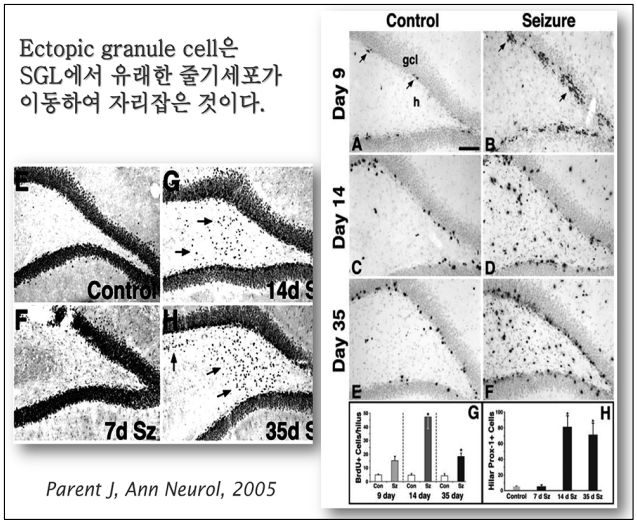


Ectopic granule cell의 역할

- Substantial number (x10 of normal)
- Faucity of inhibitory synapse
- Hyperexcitable neurons
- Formation of aberrant circuits
- Replacement of inhibitory neuronal loss



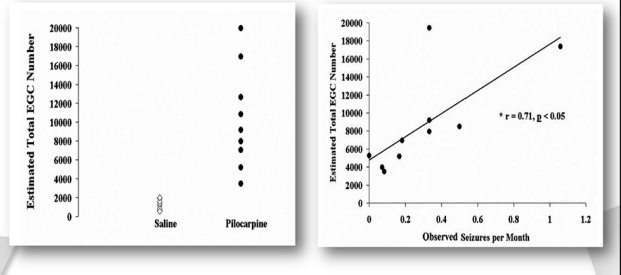
Ectopic granule cell은
SGL에서 유래한 줄기세포가
이동하여 자리잡은 것이다.



Parent J, Ann Neurol, 2005

EGCs vs SRS formation

SRS means 'spontaneous recurrent seizures'.

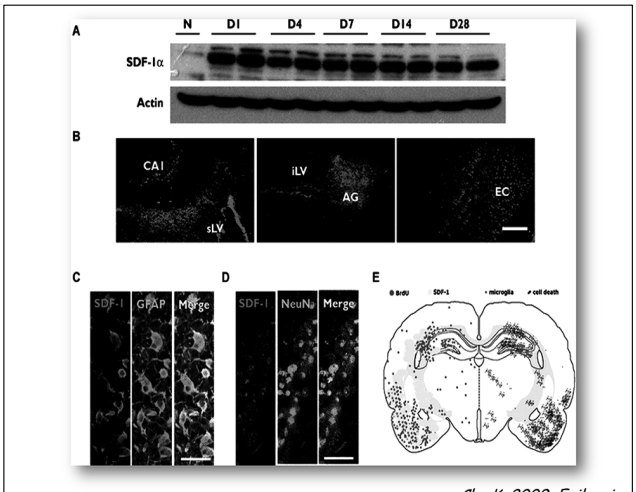


Eur J Neurosci (2006) McCloskey DP et al.

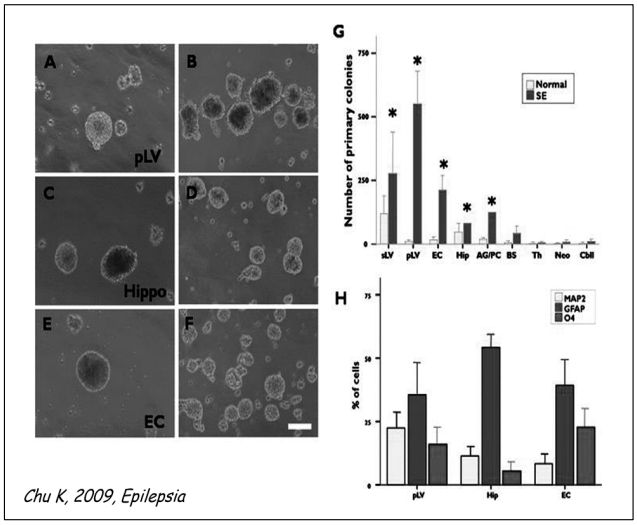
WIDESPREAD CHANGES OCCUR

NEUROGENESIS
INFLAMMATION
CELL DEATH

EPILEPTOGENESIS



Chu K, 2009, Epilepsia

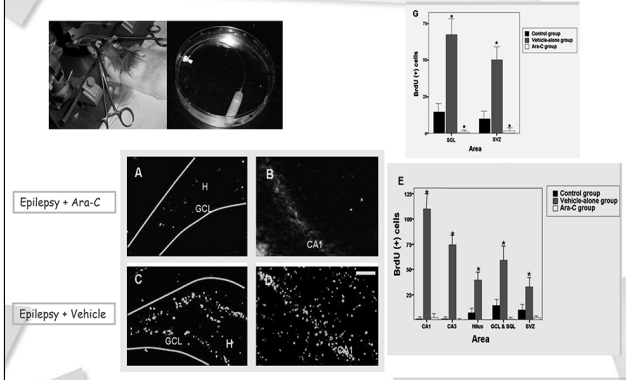


Chu K, 2009, Epilepsia

ABLATION OF NEUROGENESIS

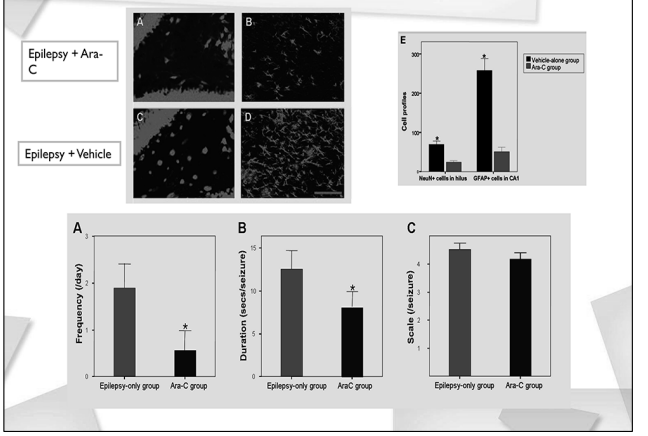
EFFECT ON EPILEPTOGENESIS

Pro-epileptogenic roles of EGCs



Eur J Neurosci (2004) Jung KH and Chu K

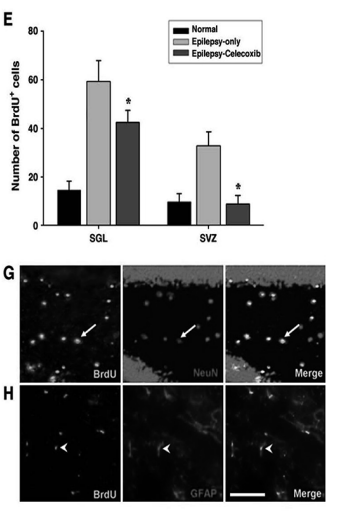
Knockdown of cell proliferation by intraventricular Ara-C infusion

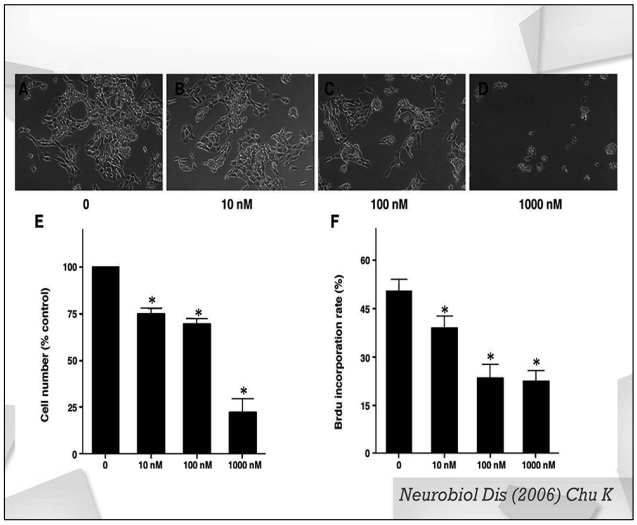


ENTAILING INFLAMMATION

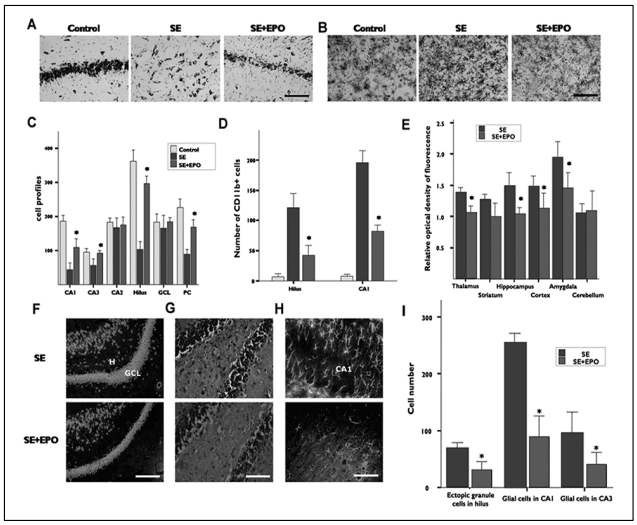
COX2

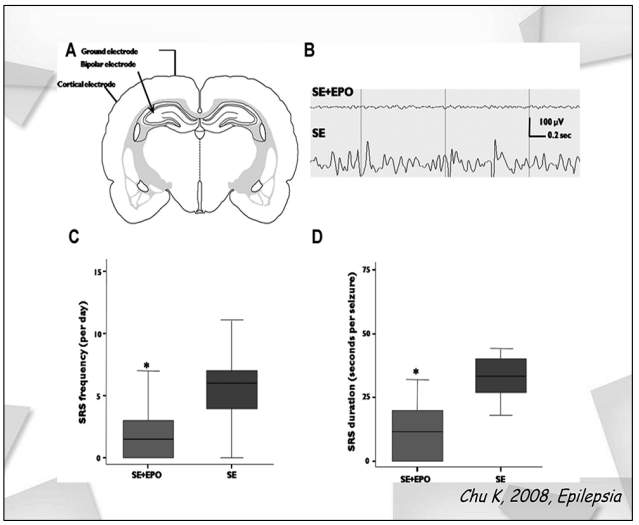
Celecoxib



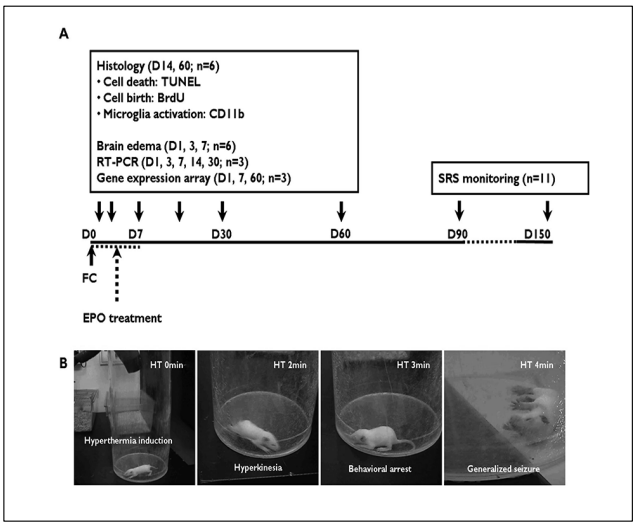

A
B
C
D
0
10 nM
100 nM
1000 nM
E
Cell number (% control)
F
Brdu incorporation rate (%)
Neurobiol Dis (2006) Chu K

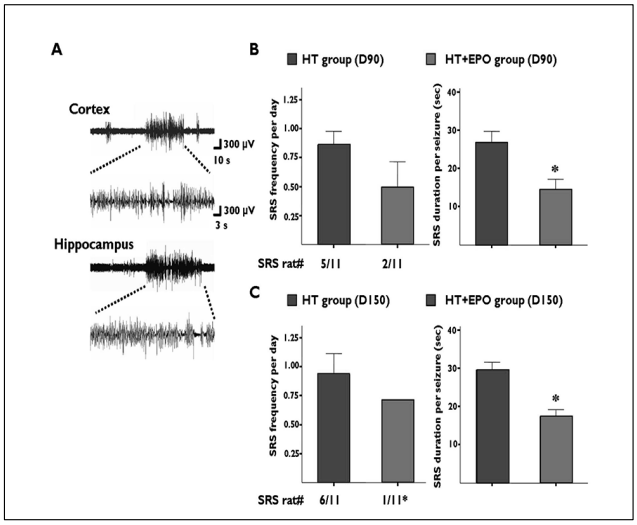

BEYOND INFLAMMATION
ERYTHROPOIETIN

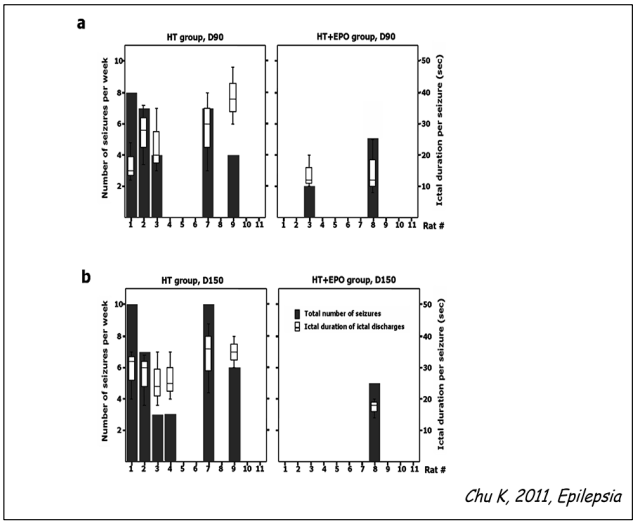

A
Control
SE
SE+EPO
B
C
cell profiles
D
Number of CD11b+ cells
E
Relative optical density of fluorescence
F
G
H
I
Cell number
Ectopic granule cells in hilus
Glial cells in CA1
Glial cells in CA3


A
Ground electrode
Bipolar electrode
Cortical electrode
B
SE+EPO
SE
100 μV
0.2 sec
C
SRS frequency (per day)
D
SRS duration (seconds per seizure)
Chu K, 2008, Epilepsia


FEBRILE SEIZURES


A
Histology (D14, 60; n=6)
• Cell death: TUNEL
• Cell birth: BrdU
• Microglia activation: CD11b
Brain edema (D1, 3, 7; n=6)
RT-PCR (D1, 3, 7, 14, 30; n=3)
Gene expression array (D1, 7, 60; n=3)
SRS monitoring (n=11)
D0
D7
D30
D60
D90
D150
FC
EPO treatment
B
HT 0min
HT 2min
HT 3min
HT 4min
Hyperthermia induction
Hyperkinesia
Behavioral arrest
Generalized seizure





Chu K, 2011, Epilepsia

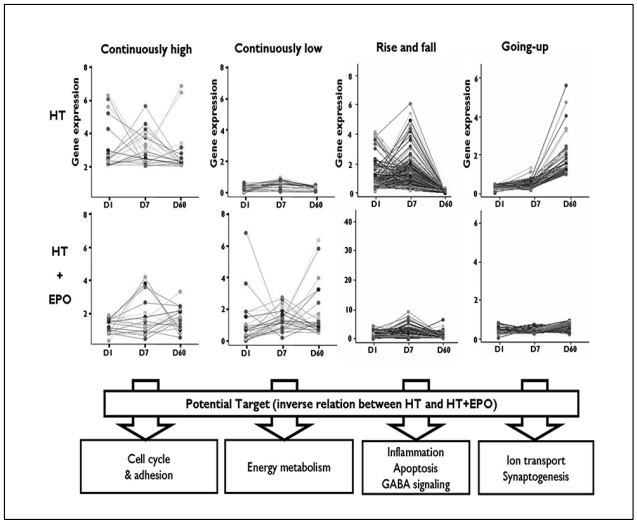
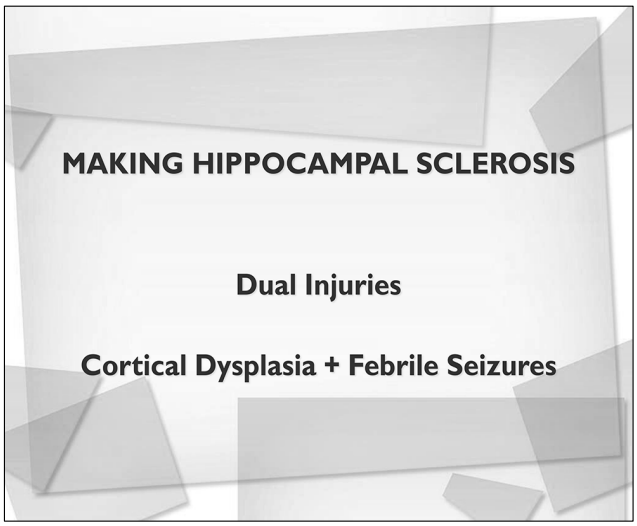
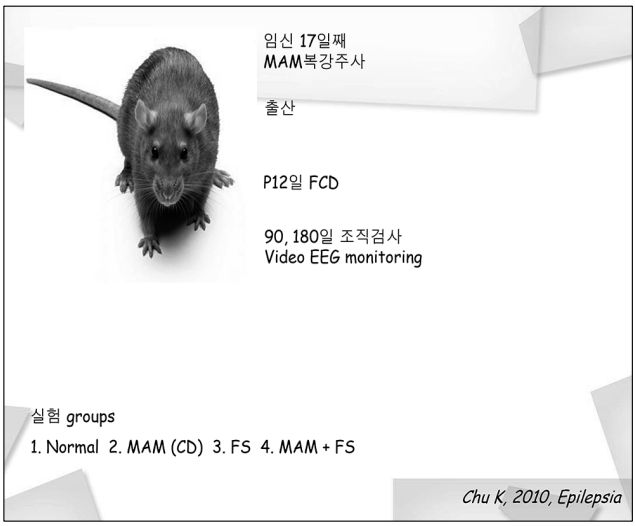


Table 4. Summary of treatments showing antiepileptogenic effects or reduction in seizure susceptibility

SE	TBI	Hyperthermia	Cortical malformation	Genetic
Atipamezole	SR141716A (Rimonabant)	SR141716A (Rimonabant)	Rapamycin	Levetiracetam
Celecoxib	Minozac			Ethosuximide
	Ceftriaxone			Zonisamide
α_4 Integrin specific mAb	Rapamycin			Vigabatrin
Erythropoietin				Rapamycin
FGF-2 and BDNF gene therapy				
Rapamycin				
Parecoxib				
NRSE-sequence decoy oligodeoxynucleotides				
Aspirin				
Fingolimod (FTY720)				
Pentylenetetrazol				
Adenosine				
Melatonin				
1NMPP1				
WP1066				

Pitkanen A, 2015, Cold Spring Harbor Perspectives in Medicine





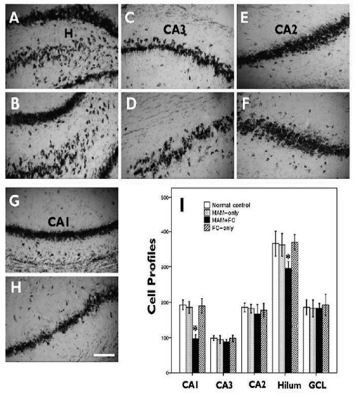
Chu K, 2010, Epilepsia

Hippocampal sclerosis는 왜 생기는 것일까?

- Febrile seizure는 흔하다.
- 그 중 아주 일부만 나중에 TLE가 된다.
- mTLE surgical specimen에서 상당수에서 cortical dysplasia가 동반되어 있다 (MRI에 보이는 경우 또는 안 보이는 경우)
- Cortical dysplasia자체가 HS를 만드는 것은 아니다.
- mTLE는 病所가 서서히 악화되는 특징이 있다.
- Febrile seizure외에도 다른 predisposing factors가 알려져 있다.

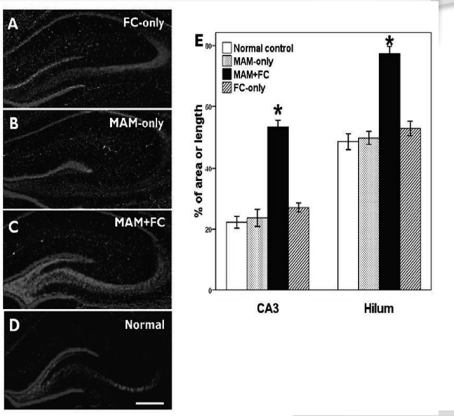
Progressive nature of hippocampal sclerosis

Hippocampal cell death after dual injuries

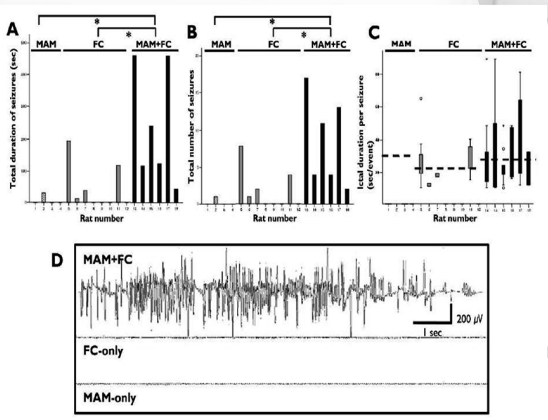


Park KI & Chu K, 2010, Epilepsia

Dual injuries remodeled hippocampus



Park KI & Chu K, 2010, Epilepsia



Park KI & Chu K, 2010, Epilepsia

MDR EPILEPSY

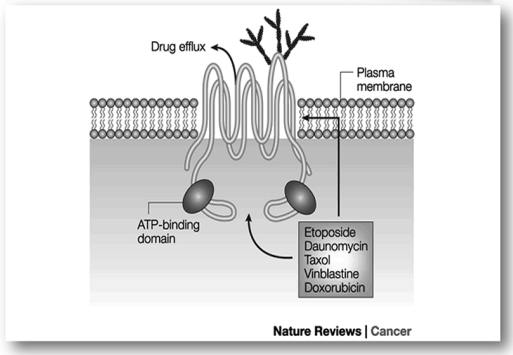
P-Glycoprotein
Epigenetic Changes

Pharmacoresistant epilepsy models

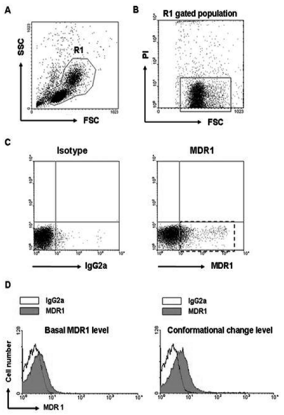
- DPH-resistant kindled rat
- CBM-resistant kindled rat
- 6Hz-psychomotor seizure model
- Post-status epilepticus-induced spontaneous seizures
- In vitro low magnesium hippocampal slice preparation
- Post-SE-SRS plus two broad spectrum AED-resistant seizure model

신경과 주건

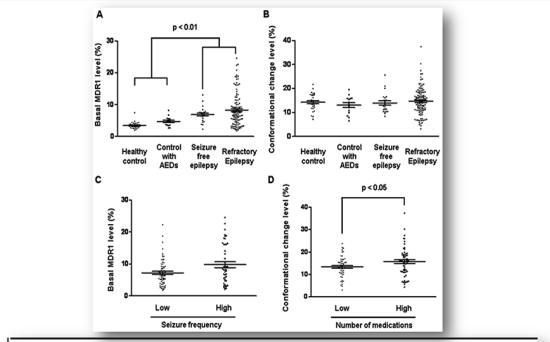
P-glycoprotein



Analysis of MDR1 profiles of PBMNCs with the flow cytometry



Chu K, 2012, PLOS One

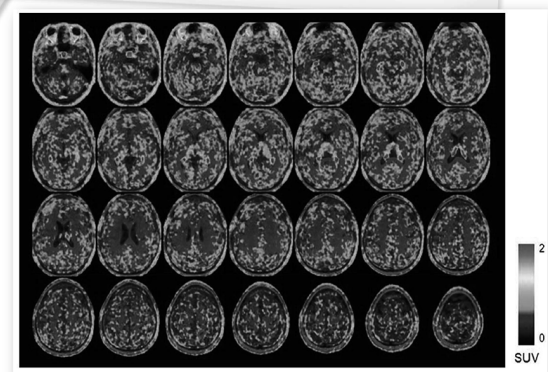


Seizure frequency			Medication number		
Factors	**Odd ratio (95% CI)**	***p* Value**	**Factors**	**Odd ratio (95% CI)**	***p* Value**
Temporal lobectomy	12.093 (2.197–66.55)	0.004	Epilepsy duration	1.06 (1–1.116)	0.017
Medication number	2.751 (1.161–6.521)	0.022	Onset age	0.99 (0.99–1)	0.838
Basal MDR1 level	1.16 (1.060–1.268)	0.001	MDR1 conformational change	1.11 (1.02–1.2)	0.008

CI = Confidence interval.
doi:10.1371/journal.pone.0036985.t004

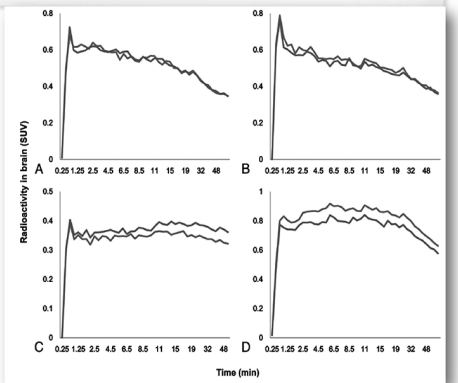
Chu K, 2012, PLOS One

(R)-[11C]-verapamil PET/MR

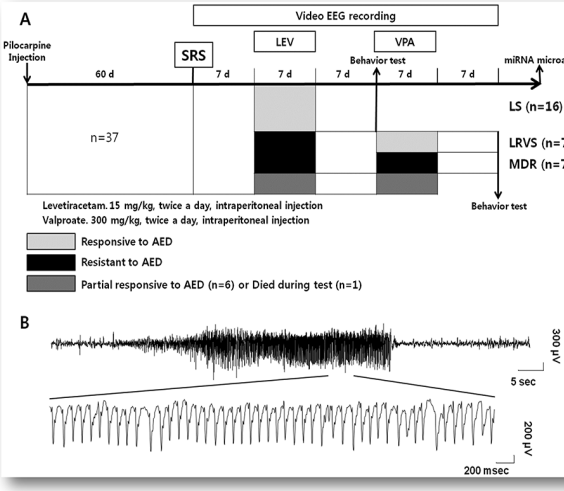


Shin JW, Chu K, 2015, AJNR

Time activity curves



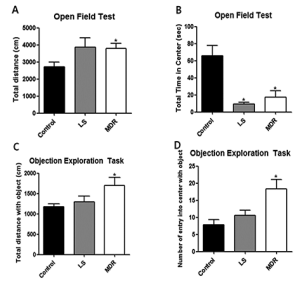
Shin JW, Chu K, 2015, AJNR



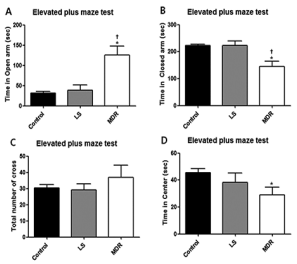
Group	Baseline	LEV	Washout	VPA
LS (n = 16)	4.29±0.84	0.29±0.12*	4.96±0.7	
LRVS (n = 7)	4.09±1.11	5.41±1.31	5±1.17	0.41±0.35**
MDR (n = 7)	3.57±1.01	6.84±1.64	4.05±0.99	6.01±1.31

All data are presented as mean ± standard error of mean (SEM).
Abbreviations: AED: antiepileptic drug, LEV: levetiracetam, VPA: valproate, LS: levetiracetam sensitive, LRVS: levetiracetam resistant/valproate sensitive, MDR: multidrug resistant.
(*) and (**) represent significant difference between AED trial with its respective baseline ($p<0.001$ and $p<0.05$, respectively, Mann-Whitney U test).
doi:10.1371/journal.pone.0085617.t001

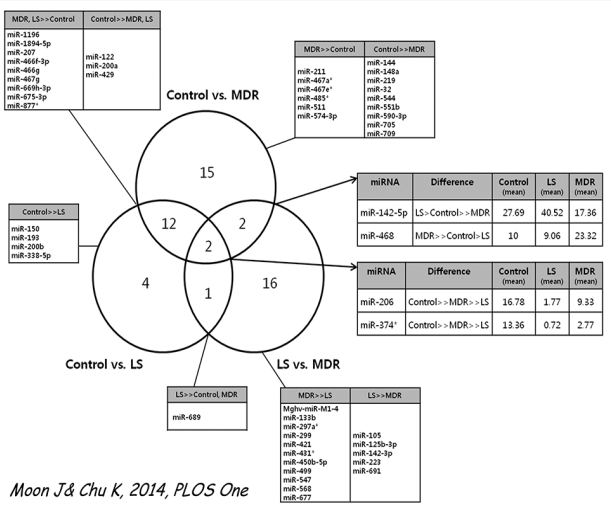
Moon J& Chu K, 2014, PLOS One



MDR group alone showed increased locomotor or exploratory activity compared to the control or LS groups



impairment of their risk assessment and decision-making ability, rather than anxiety-like behavior



miRNA	Difference	Control (mean)	LS (mean)	MDR (mean)
miR-142-5p	LS>Control>>MDR	27.69	40.52	17.36
miR-468	MDR>>Control>LS	10	9.06	23.32

miRNA	Difference	Control (mean)	LS (mean)	MDR (mean)
miR-206	Control>>MDR>>LS	16.78	1.77	9.33
miR-374*	Control>>MDR>>LS	13.36	0.72	2.77

Moon J& Chu K, 2014, PLOS One