The Epilepsy Clinic
Dep. Of Clinical Neurophysiology
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Pharmacological refractoriness in Status Epilepticus

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Reasons for medical refractoriness

- Drug does not reach target (Transport hypothesis)

- Drug loose efficacy on its receptor (Target hypothesis)

Evidence of medical refractoriness in Status Epilepticus?

- Clinical experience: Common problem, SE > 30 min difficult to control
- In Glostrup: Approx. 30 ptt/yr with SE refract. on 1st and 2nd drug
- Several human studies show that delayed treatment ⇨ response to treatment ↓ prognosis ↓
- Animal models: Chemical/electrically induced SE, can initially be blocked by GABA'ergic drugs, but later (~30 min) GABA drugs loose potency (20-30x)
- Brain tissue models: Sz. like activity initially blocked by AEDs, but later (~2 hrs.) no effect of AEDs

What are the mechanisms of medical refractoriness in SE ??

- Primarily experimental data available, suggesting several mechanisms, lack of human data …

- Rapid occurring events (min/hrs), i.e. not likely dependent on gene transcription, tissue plasticity etc.

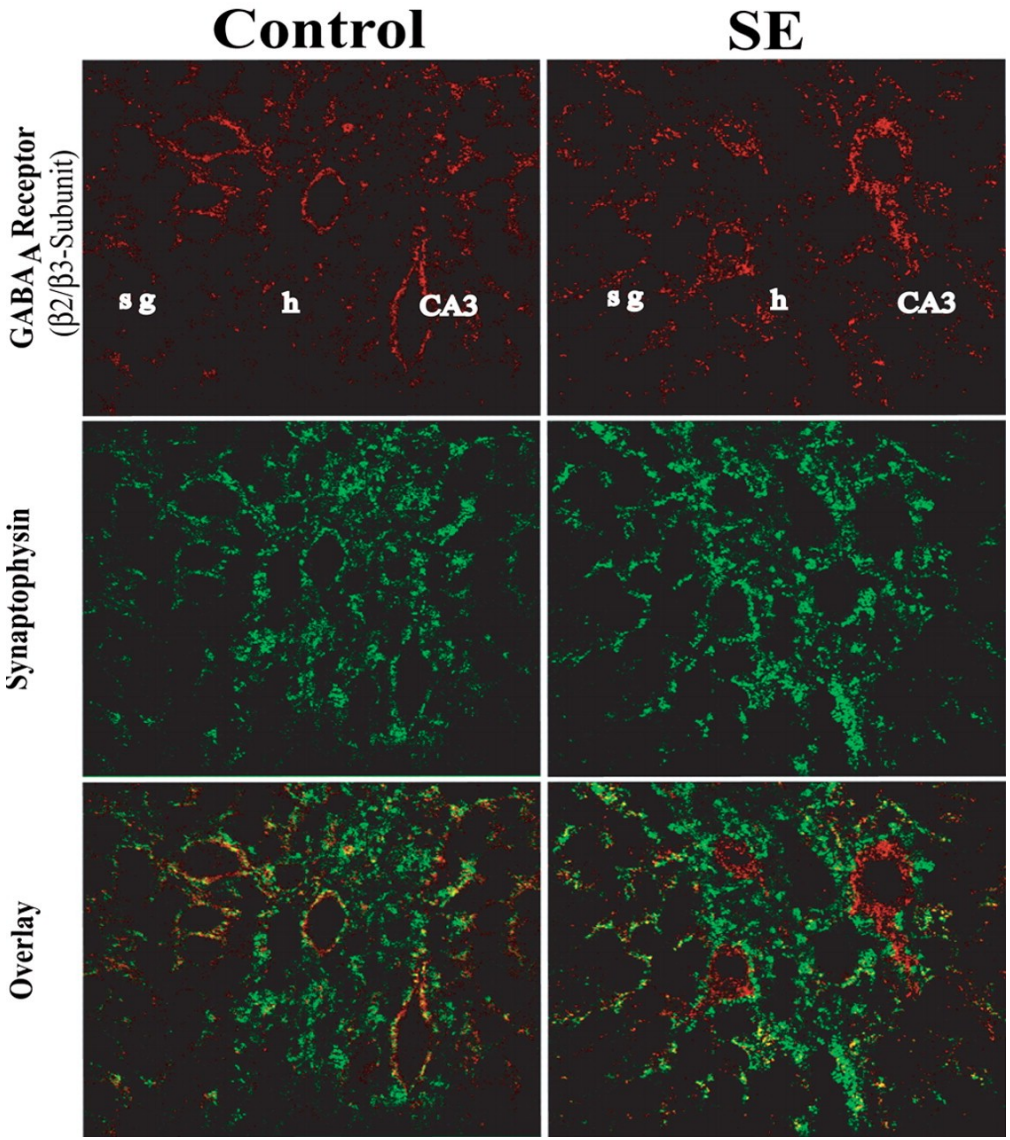
What are the mechanisms of medical refractoriness in SE ??

- Receptor trafficking ($GABA_A$, AMPA)
- Mods in Neuropeptide expression (galanin, substance P)
- Mods in Drug transport proteins (P-gp)

More speculative mechanisms …

- Cerebral oedema in SE ⇨ sequestering AED in perivascular tissue
- Metabolic (mitochondrial) dysfunction
  - ATP decrease
  - Oxidative stress, and ROS ↑ (free radicals)
  - Potential mods in target molecules
- Inflammation lower seizure threshold (in rodents)

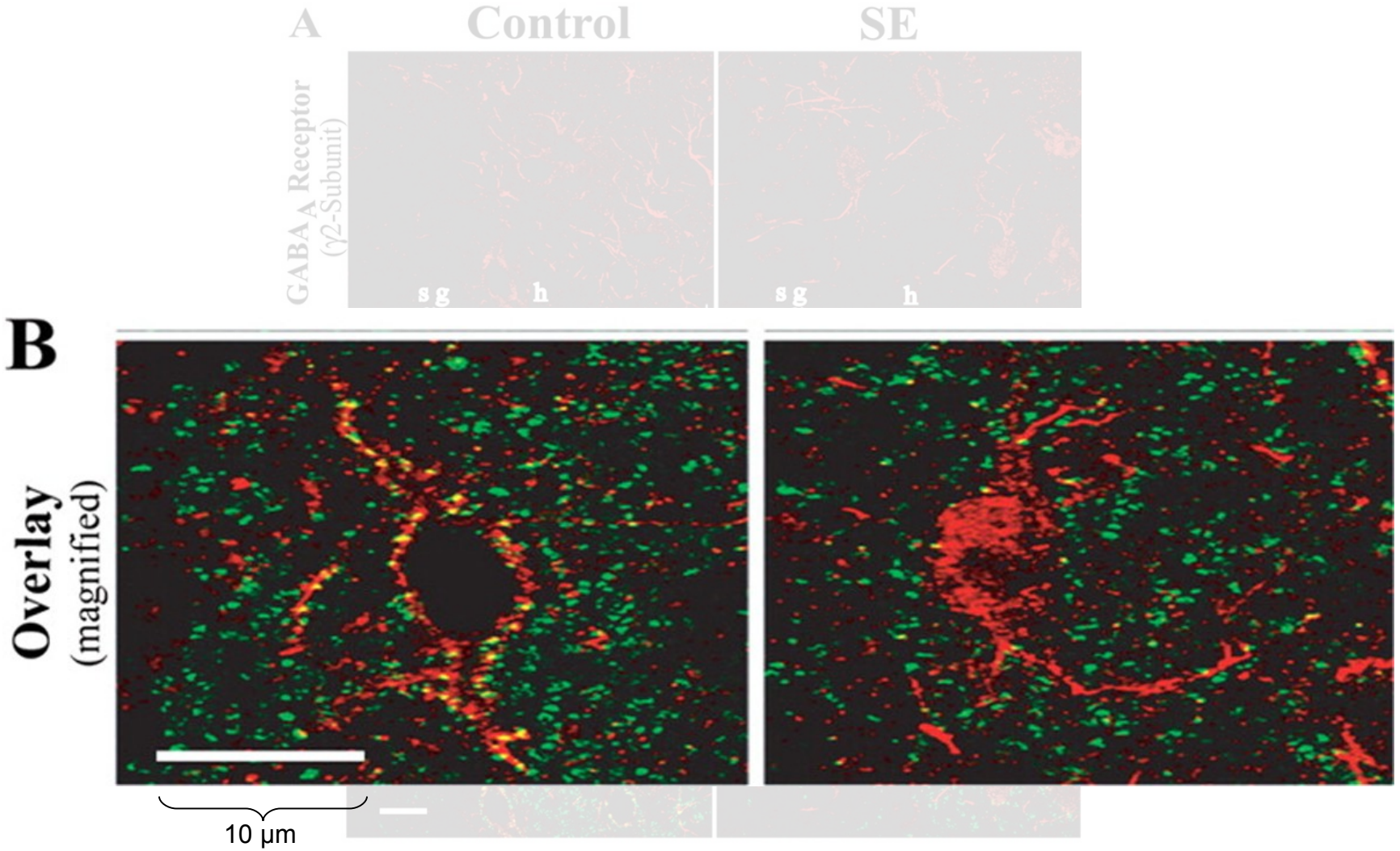
Receptor trafficking



- Rodents, pilocarpine induced SE
- Decap after 1hrs SE
- Hippocampal tissue sections
- Immunohistochemical stains
- Similar changes seen with NMDA receptors in the opposite direction

Naylor et al., Jr of Neuroscience, 2005

Receptor trafficking

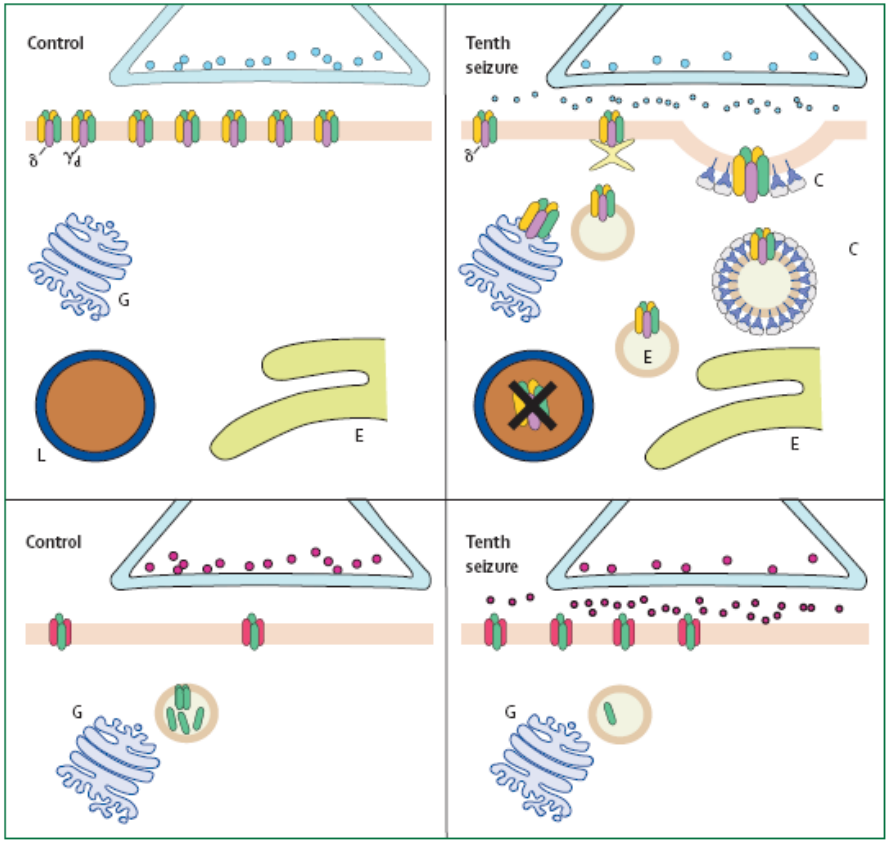


Naylor et al., Jr of Neuroscience, 2005

Receptor trafficking (math model)

GABA$_A$ receptorer

NMDA receptorer

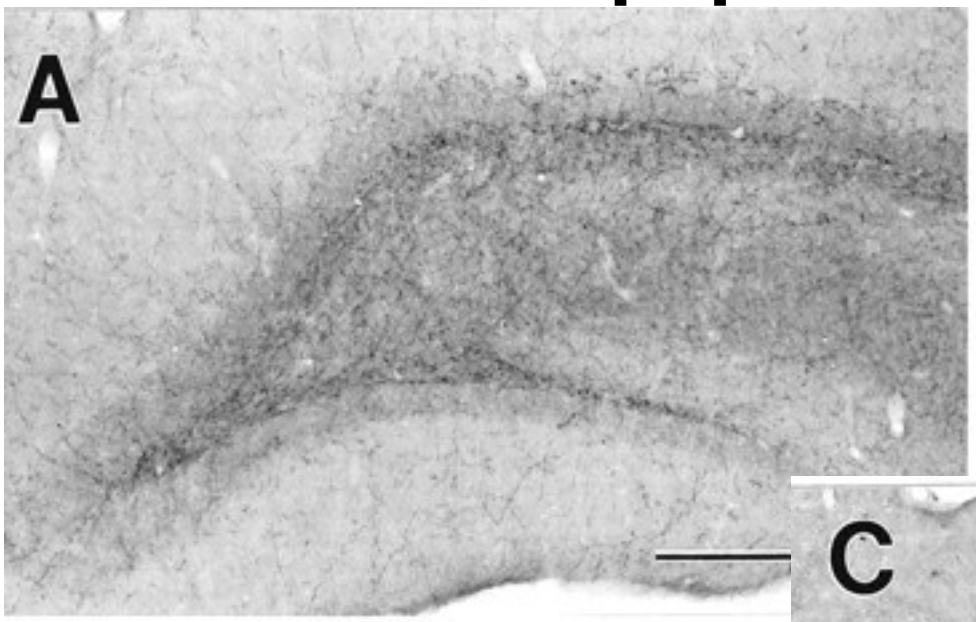


C: Clathrin-Coated Vesicles
E: Endosomes
L: Lysosomes
G: Golgi apparatus

Equilibrium shifts towards a excitatory state with relative GABA insensitivity

Naylor et al., Jr of Neuroscience, 2005
Chen & Wasterlain, The Lancet, 2006

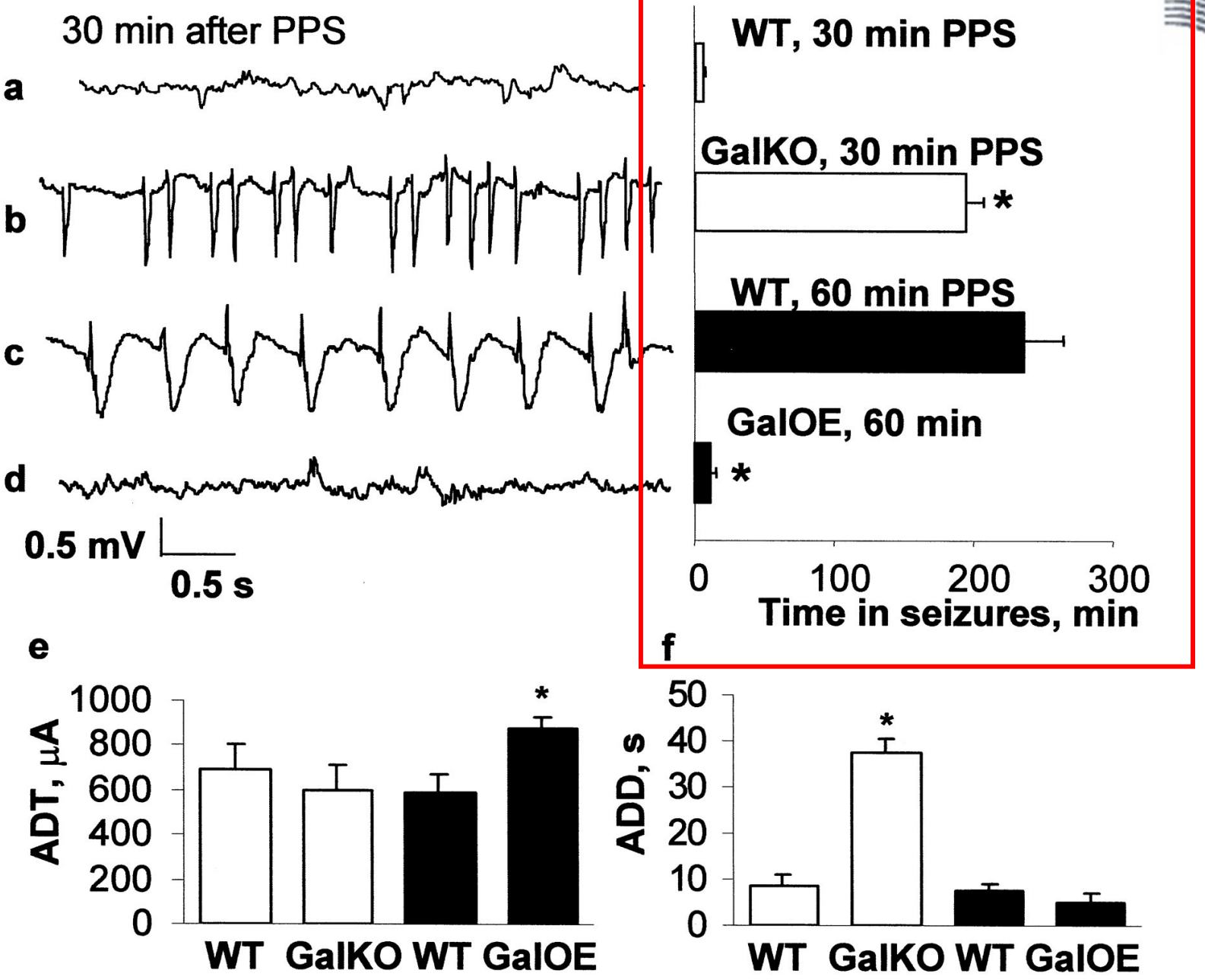
Maladaptive Modulations in Neuropeptide expression



- **Galanin** – a small peptide present in many brain structures
- Inhibitory actions in hippocampus

- Rodents, electrically induced SE (PPS)
- Galanin fibers in hippocampus in
  A. Controls
  C. SE animals 12hrs after SE
- Depletion of Galanin containing fibers

Mazarati et al., Jr of Neuroscience, 1998

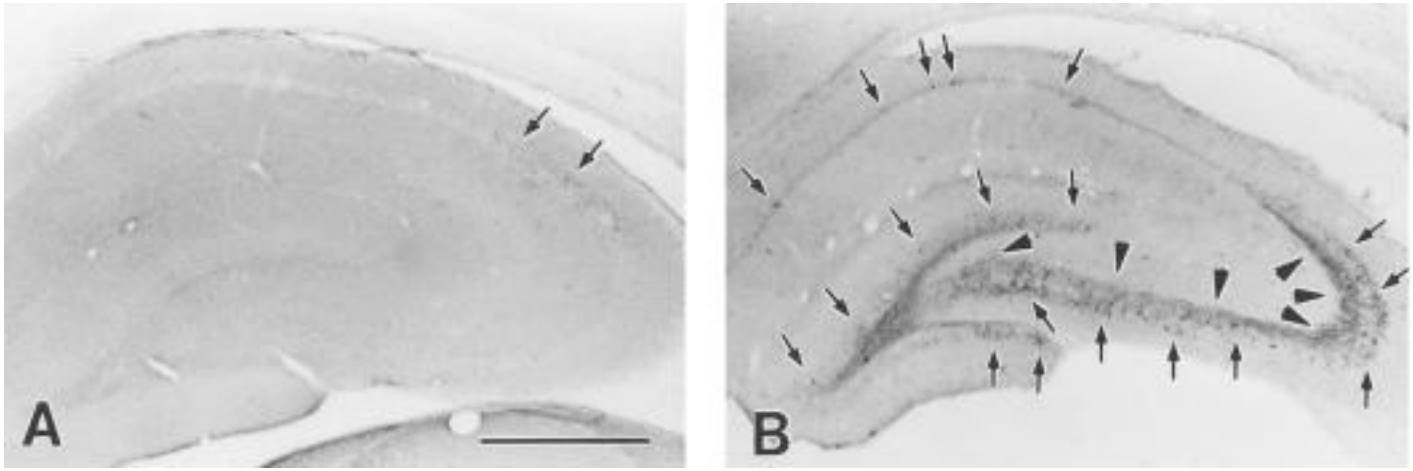


Mazarati et al., Jr of Neuroscience, 2000

Maladaptive Modulations in Neuropeptide expression

- Substance P – neuropeptide with excitatory actions
- In control animals not expressed in hippocampus (A)

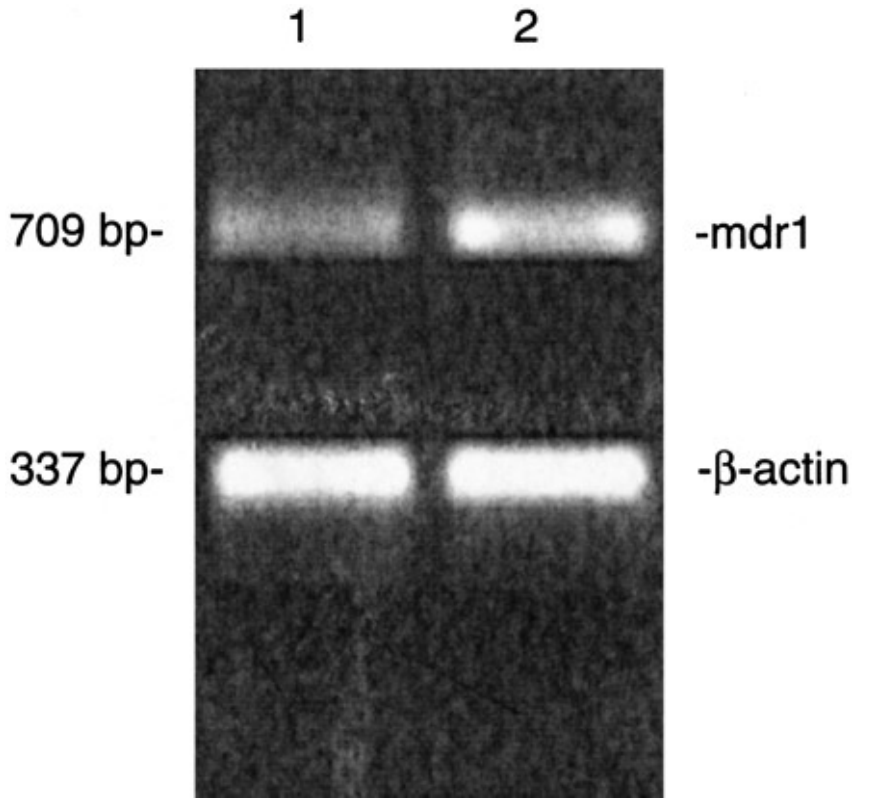
- Rodents, electrically induced SE (PPS)
- Dramatic increase in SP fibers 24hrs after SE



Liu et al., Proc Natl Acad Sci, 1999

Maladaptive Modulations in Drug transport proteins

- Permeability glycoprotein (P-gp) a membrane located transporter with affinity for several drugs / AEDs (PHT; PHB)
- Rodents, kainic acid induced SE
- Gene coding for P-gp mRNA up regulated after 3-6 hrs post SE



Rizzi et al., Jr of Neuroscience, 2002

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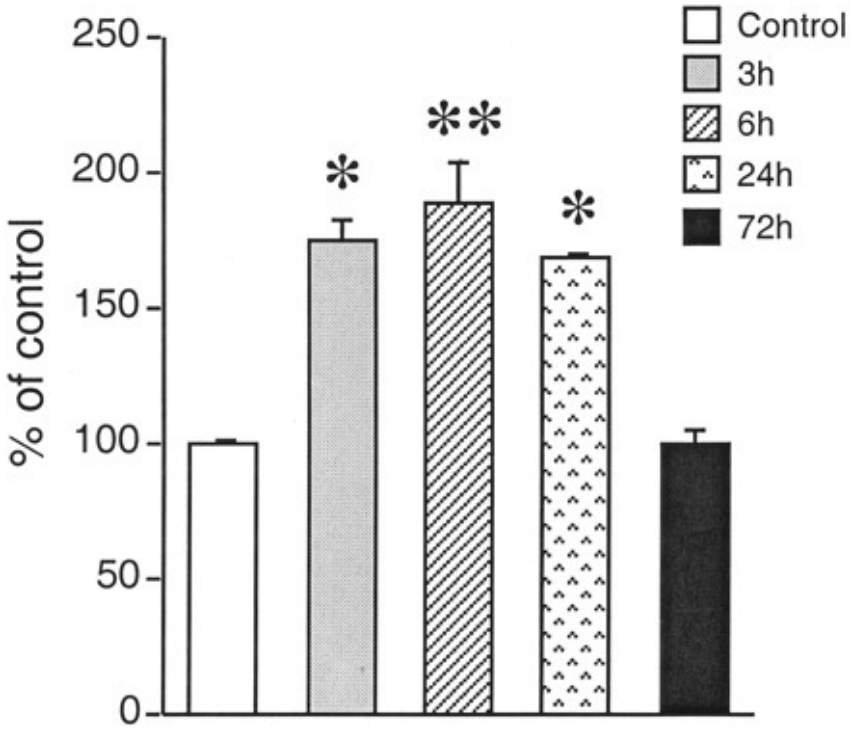

Upregulation of P-gp expels drug from CNS

Rizzi et al., Jr of Neuroscience, 2002

Maladaptive Modulations in Drug transport proteins

- Transgenic mice with defect P-gp gene vs. WT mice :

Table 3. Plasma and tissue concentrations of phenytoin and carbamazepine in *mdr1* −/− mice and their wild-type littermates

Drug	Time (hr)	Genetic status	AED concentrations (µg/ml or gm)		
			Hippocampus	Plasma	Ratio[c]
Phenytoin[a]	1	Wild type	26.4 ± 1.0	17.8 ± 0.5	1.5 ± 0.1
		mdr1a/b −/−	38.2 ± 2.4*	16.5 ± 1.0	2.4 ± 0.3*
	4	Wild type	7.1 ± 0.5	12.9 ± 0.4	0.5 ± 0.0
		mdr1a/b −/−	10.4 ± 0.6*	13.2 ± 0.5	0.8 ± 0.1*
Carbamazepine[b]	1	Wild type	8.4 ± 1.0	3.9 ± 0.4	2.2 ± 0.0
			(1.2 ± 0.1)	(0.8 ± 0.1)	(1.5 ± 0.1)
		mdr1a/b −/−	6.2 ± 0.8	3.2 ± 0.5	2.1 ± 0.1
			(1.4 ± 0.2)	(0.8 ± 0.1)	(2.2 ± 0.1*)
	3	Wild type	<0.5	<0.3	
			(<0.5)	(<0.3)	
		mdr1a/b −/−	1.2 ± 0.2*	0.4 ± 0.1*	2.5 ± 0.4
			(1.0 ± 0.2*)	(0.3 ± 0.1*)	(3.0 ± 0.4)

Rizzi et al., Jr of Neuroscience, 2002

Maladaptive Modulations in Drug transport proteins

- In humans overexpression of P-gp is found in surgically resected brain tissue (chronic condition)
    - Tishler et al, 1995
    - Sisodiya et al, 2001

Conclusions

- Animal data support the clinical experience that efficacy of several AEDs decrease with the duration of SE
- Several mechanisms are proposed
  - Receptor trafficking ($GABA_A$/NMDA) within 30 mins of SE onset
  - Neuropeptide depletion (Gal) and overexpression (Subst-P) within hours
  - Transport protein up regulation (P-gp) within hours
  - Mechanisms supporting both the target and the transport hypothesis
- Once SE becomes self-sustaining, a vicious circle consisting of these maladaptive mechanisms makes it increasingly difficult to overcome this process with AEDs.

Impact on current treatment strategies in SE

- Time-span crucial: Choose the right drug at the right time (treat early)
- Preferably initiate treatment with 2 drugs with different mechanisms of action
- Use sufficient drug dosages (treat aggressively)
- Inhibit drug transporters (Verapamil/P-gp)

Impact on future treatment strategies in SE

- Specific inhibitors of G-gp
- Drugs that are not substrates for G-gp
- Blocking endocytosis of $GABA_A$
- Further investigation of NMDA antagonists
- Neuropeptide receptor ligands
  - Galanin agonist?
  - Substance P antagonist?