Pathophysiology and Treatment of Refractory SE: Lessons from Animal Models

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Disclosures

Name of Commercial Interest	Type of Financial Relationship
NIH (NINDS)	**Research Grants**
VA Health Administration	**Research Grant**

FDA Approval

Midazolam, ketamine and valproate are not approved by the FDA for treatment of RSE

Learning Objectives

- Understanding some recent advances in the pathophysiology of status epilepticus

- Understanding the therapeutic implications of those basic advances

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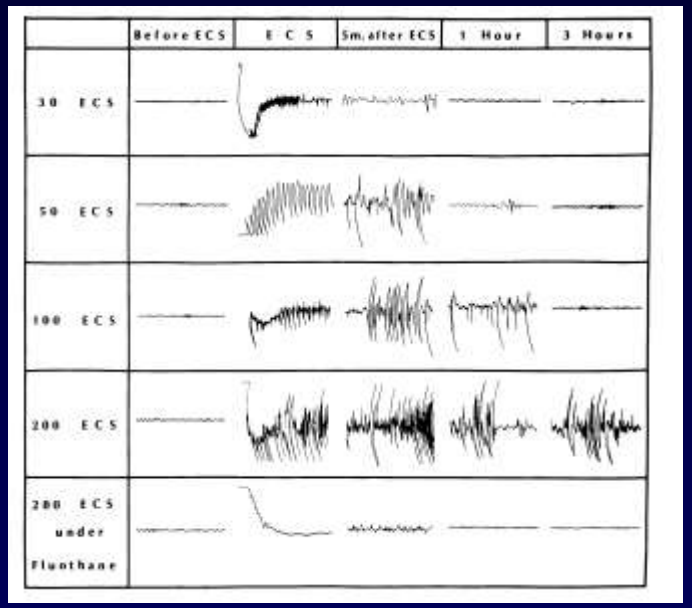
PATHOPHYSIOLOGY OF STATUS EPILEPTICUS

SEIZURES BECOME SELF-SUSTAINING AND INDEPENDENT OF THEIR ORIGINAL TRIGGER

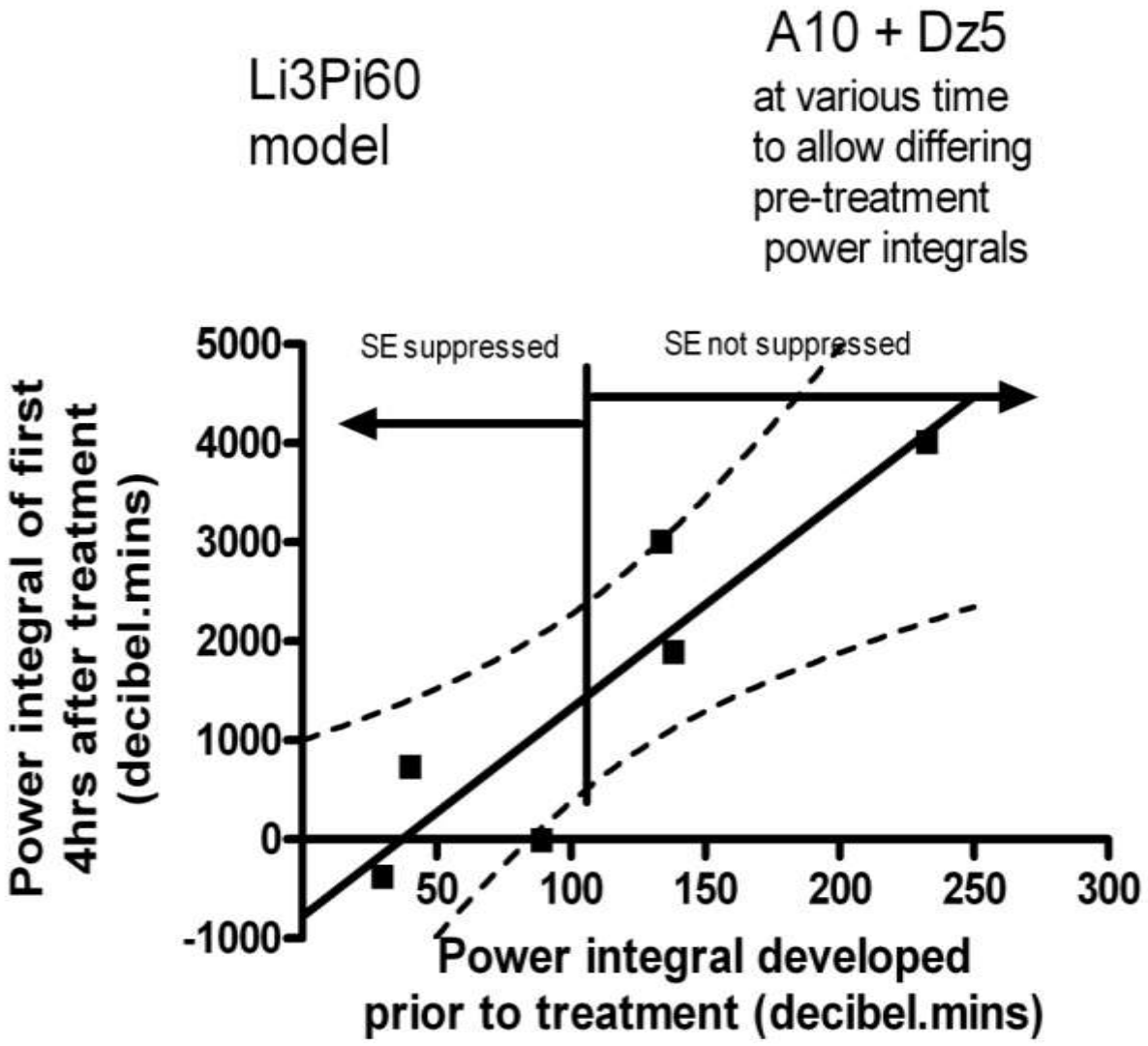
Wasterlain 1974



TIME-DEPENDENT DEVELOPMENT OF PHARMACORESISTANCE TO BENZODIAZEPINES (diazepam 5 mg/kg)

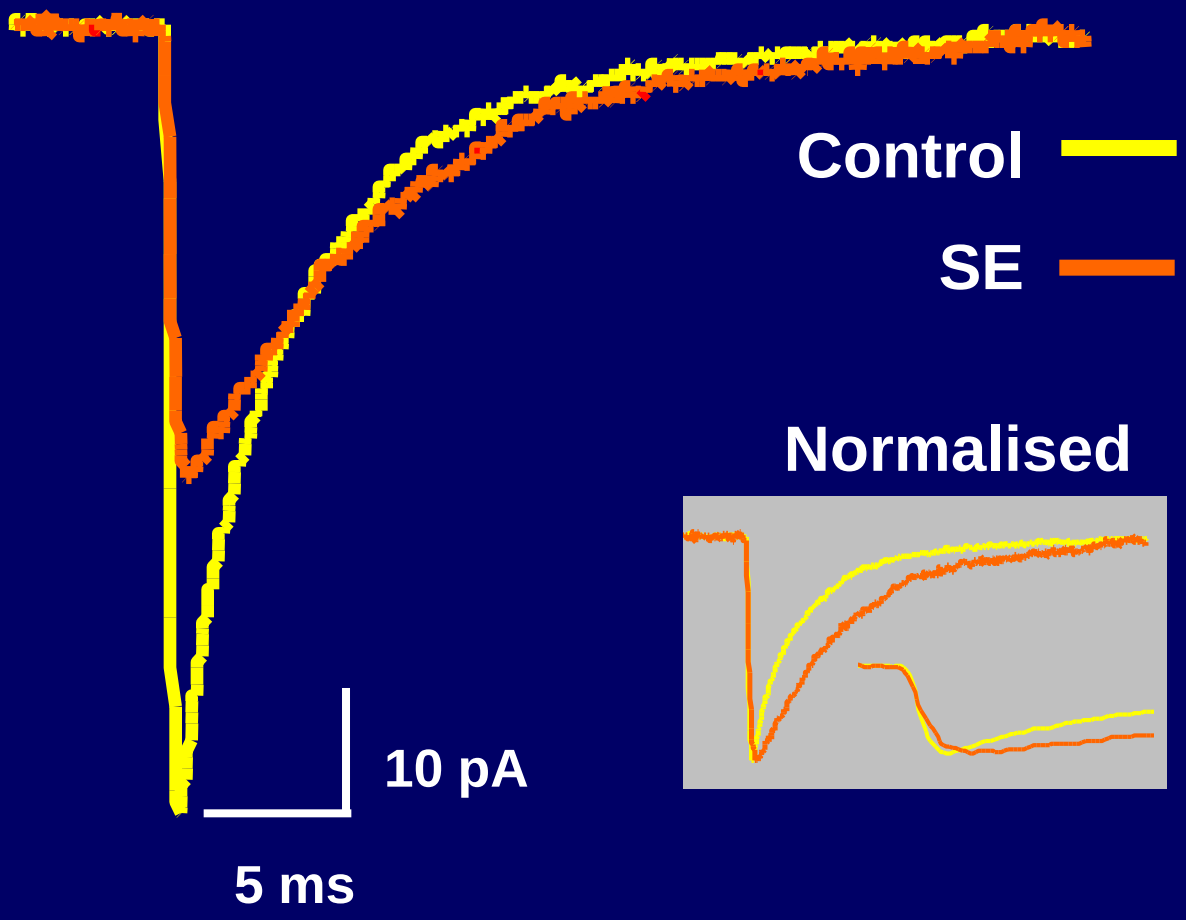
Kapur & MacDonald 1997, Mazarati et al 1998

PHARMACORESISTANCE CORRELATES WITH EEG POWER INTEGRAL BEFORE TREATMENT, SUGGESTING THAT IT IS INFLUENCED BY SEIZURE FREQUENCY AND SEVERITY



Effect of SE on miniature IPSCs

on dentate granule cell somas (after 1 hr lithium/pilocarpine SE)



Number of $GABA_A$ receptors / synapse

C: 38 ± 15

SE: 20 ± 6*

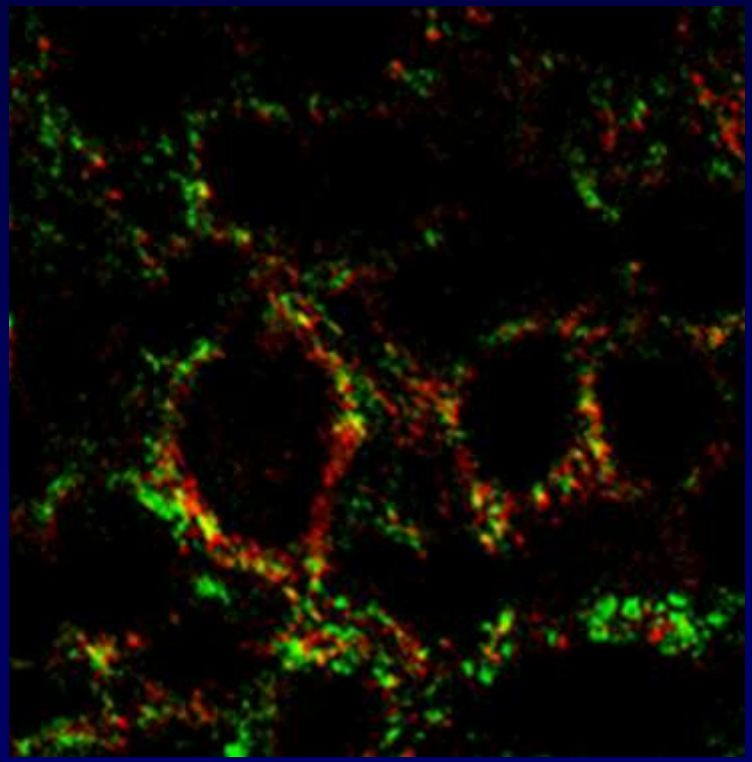
*** p < 0.001**

Naylor et al j. Neurosci.2005

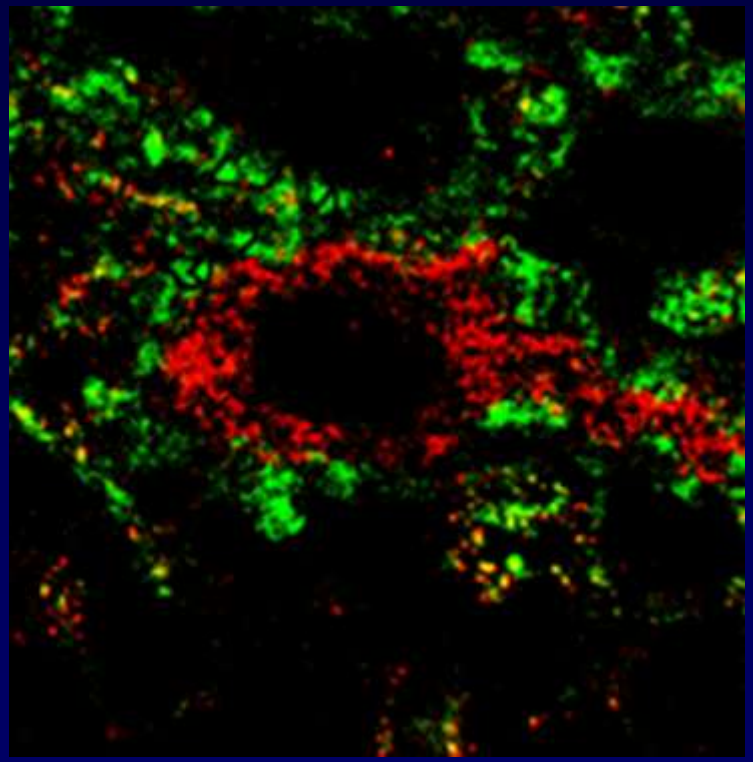
$GABA_A$ receptor trafficking

$\beta_{2/3}$ vs synaptophysin

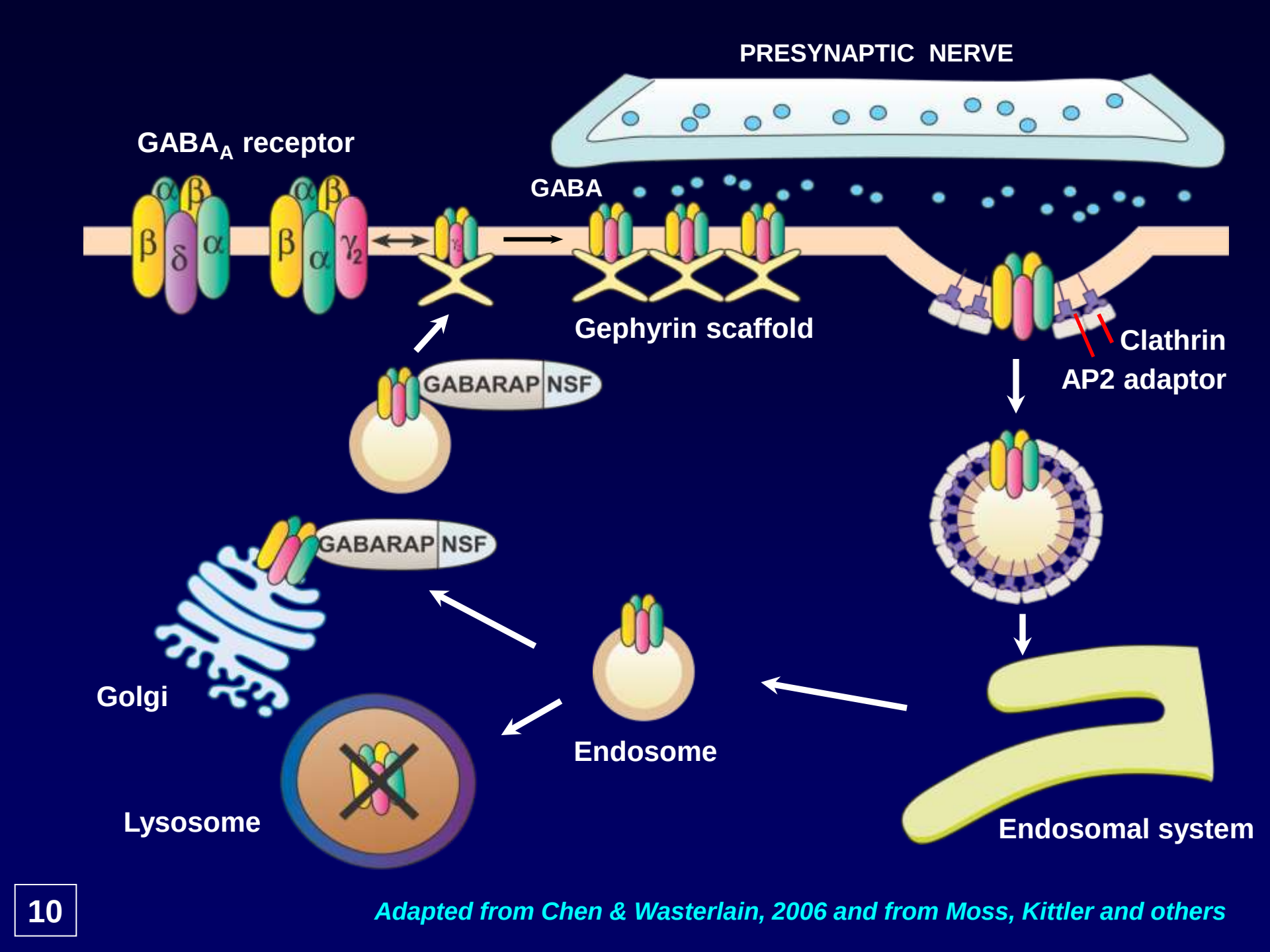
Control



SE

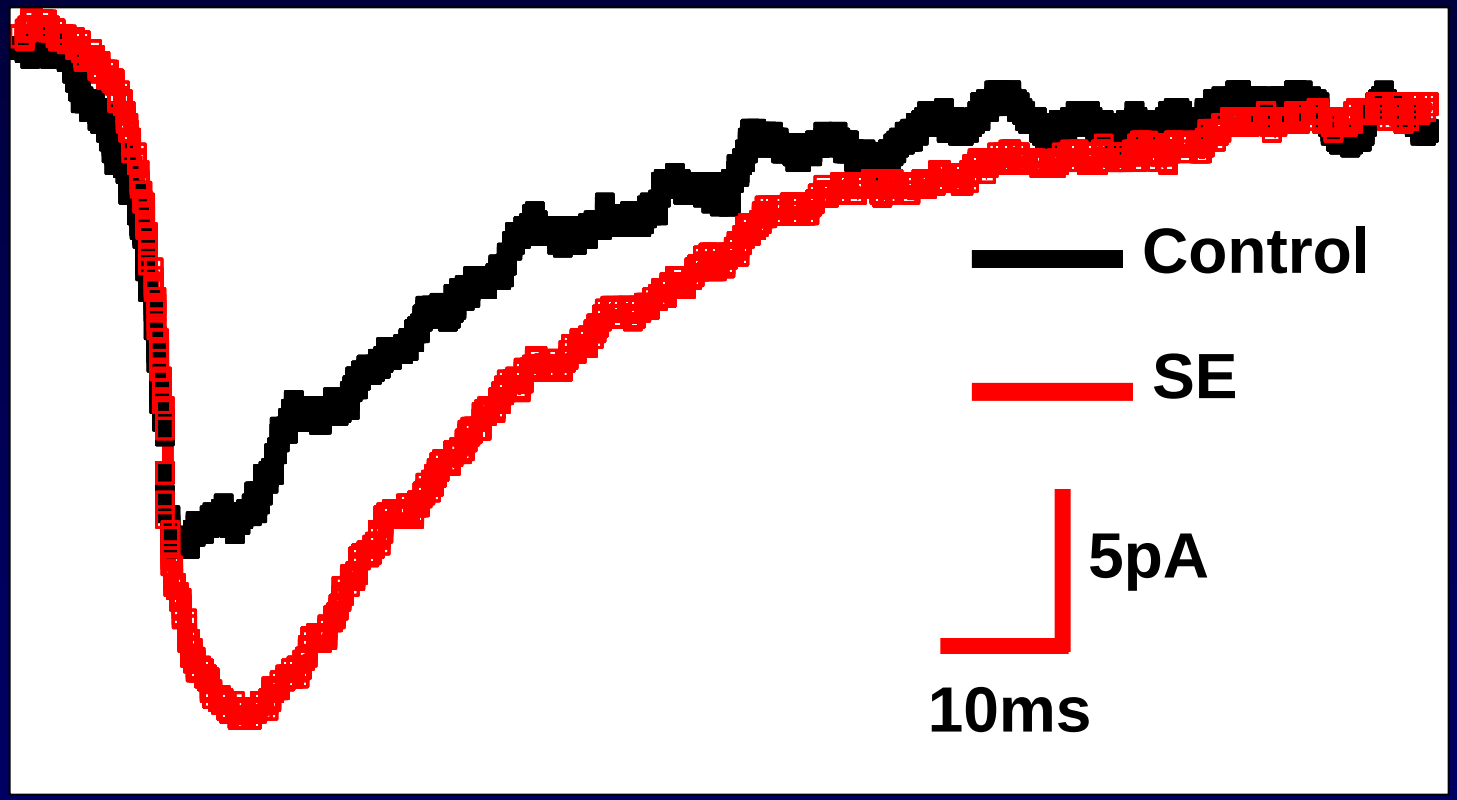


Naylor et al 2005



Adapted from Chen & Wasterlain, 2006 and from Moss, Kittler and others

Effect of SE on miniature NMDA EPSCs

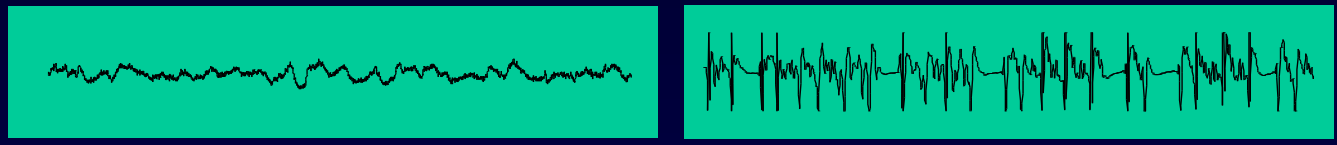


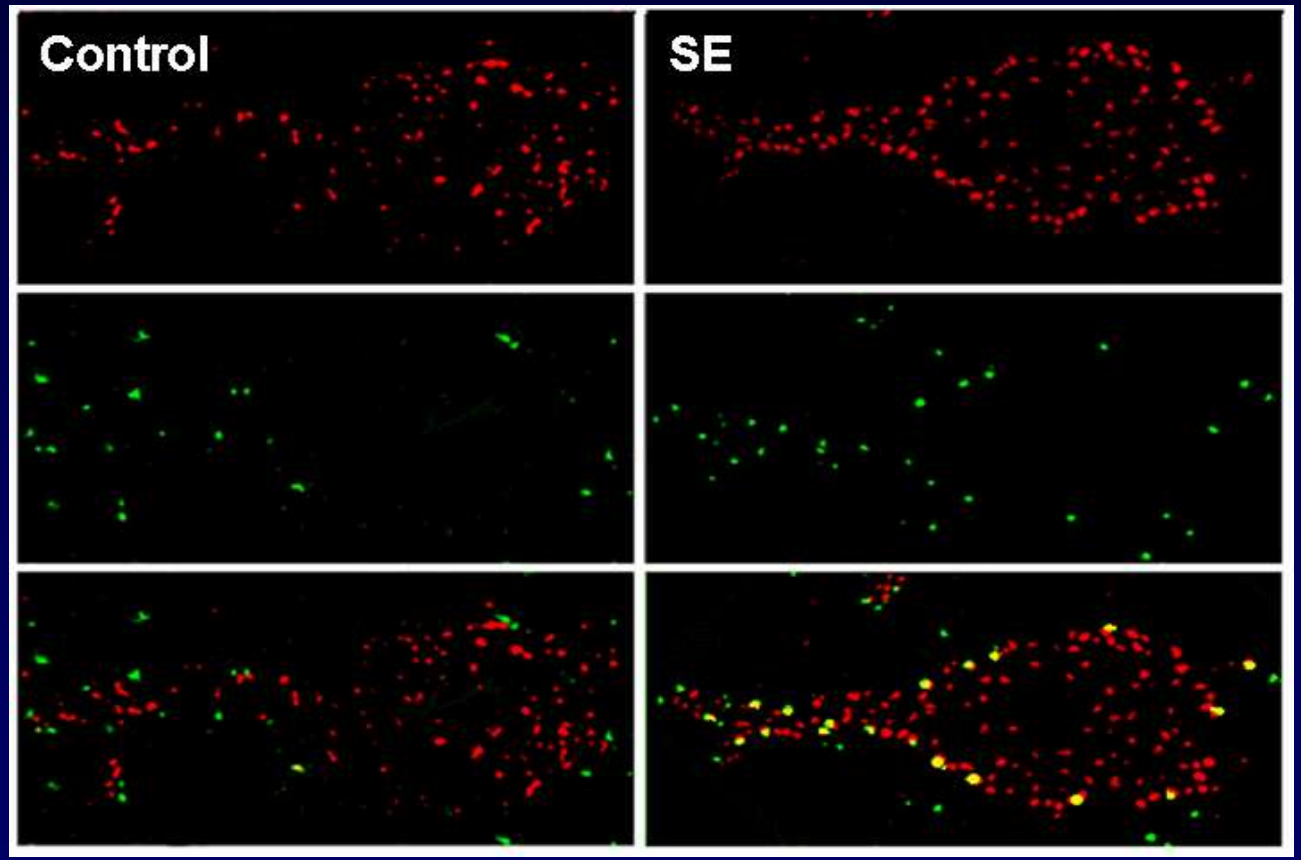
Hippocampal slices from 1 hr lithium-pilocarpine SE rats

Number of NMDA receptors / GC synapse: C 5±1, SE 8±2 ($p<0.001$)

Wasterlain et al 2002

NMDA receptor trafficking during SE





NR1 subunit

Synaptophysin

Overlay

Wasterlain & Treiman MIT Press, 2006

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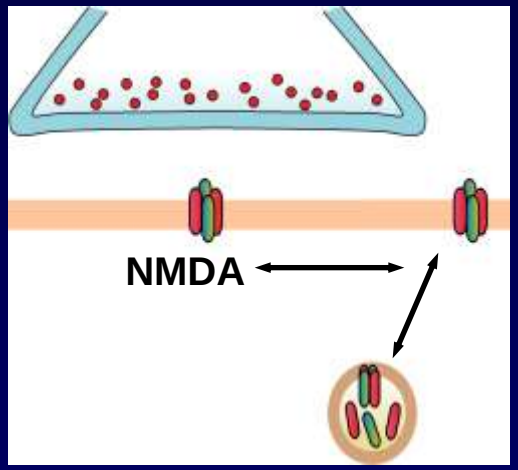
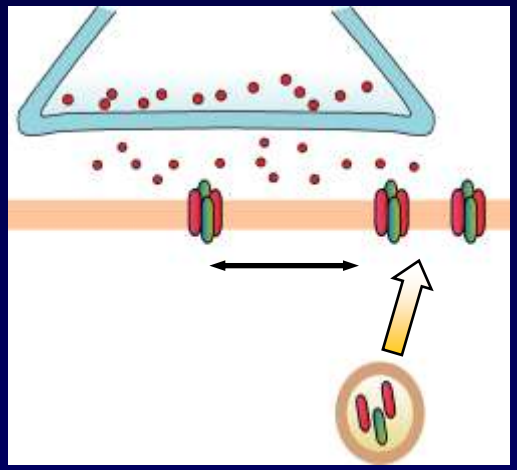
NMDA synapses

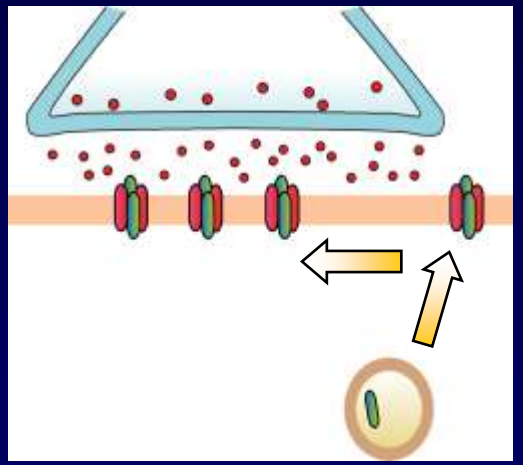
Resting



Stimulation



SE



RECEPTOR TRAFFICKING DURING SE: CAN WE REVERSE ITS CONSEQUENCES?

- REDUCED NUMBER OF SYNAPTIC $GABA_A$ R → PHARMACORESISTANCE TO BENZODIAZEPINES
- INCREASED NUMBER OF SYNAPTIC NMDAR → MAINTAIN SELF-SUSTAINING SEIZURES

- **TIME IS OF THE ESSENCE**. PHARMACORESISTANCE INCREASES WITH TIME. PRE-HOSPITAL TREATMENT SHOULD BECOME ROUTINE (RAMPARTS) THERE SHOULD BE NO TIME WASTED BETWEEN TREATMENTS

- **EARLY POLYTHERAPY:** SINCE PHARMACORESISTANCE IS TIME-DEPENDENT, WHY WAIT FOR A DRUG TO FAIL BEFORE STARTING THE NEXT ONE?

- SINCE THE NUMBER OF SYNAPTIC $GABA_A$ RECEPTORS IS REDUCED, **WE CANNOT FULLY RESTORE INHIBITION WITH $GABA_A$ AGONISTS ALONE**

- IF SE-ASSOCIATED SYNAPTIC CHANGES INVOLVE BOTH $GABA_A$ AND GLUTAMATERGIC NETWORKS, SHOULD WE **TREAT BOTH**?

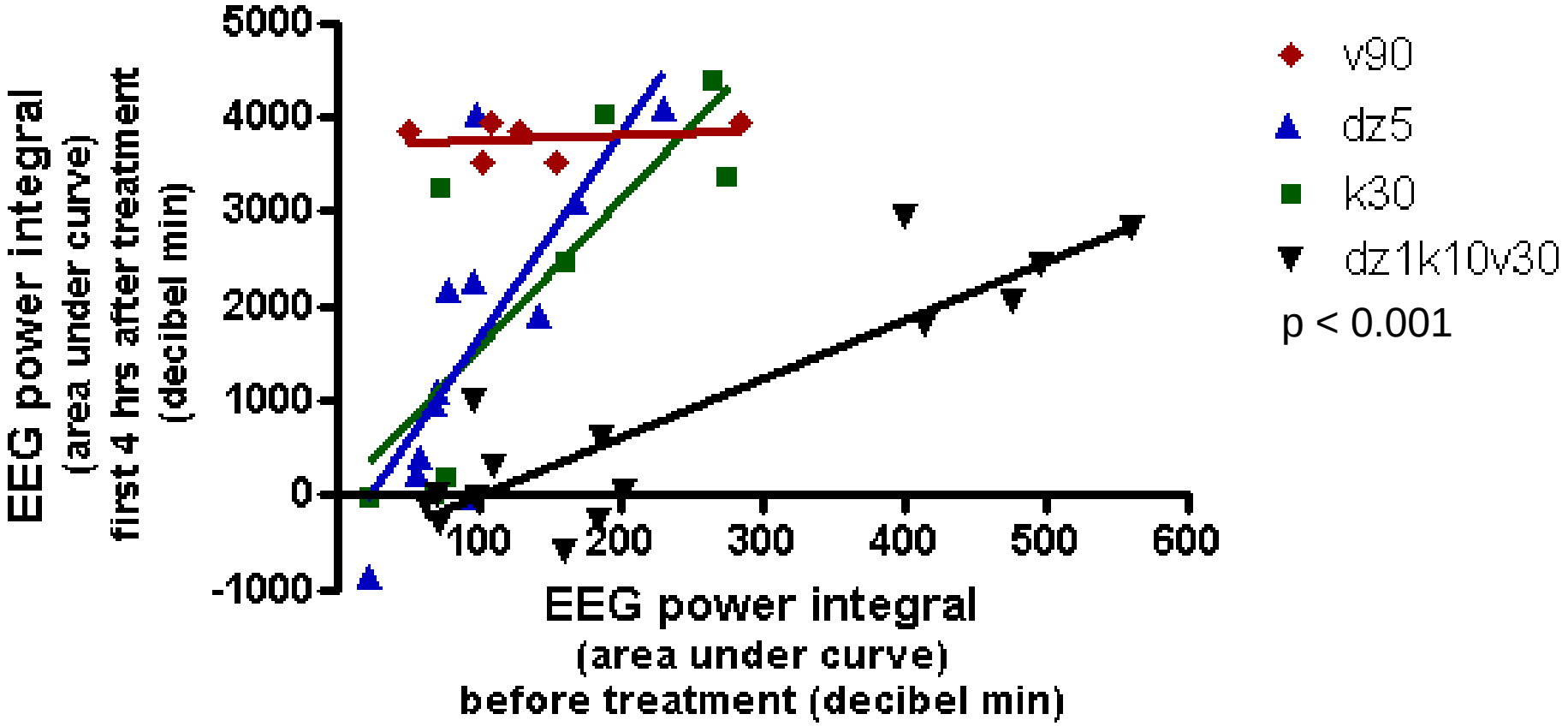
RECEPTOR TRAFFICKING DURING SE: CAN WE USE IT TO SELECT SYNERGISTIC DRUGS?

- Benzodiazepines enhance $GABA_AR$ function and can partially restore inhibition (diazepam).
- Since the number of $GABA_AR$ is reduced we should add another AED in an attempt to fully restore inhibition (valproate).
- NMDA antagonists can reduce excessive glutamatergic excitation (ketamine).
- We should replace sequential polytherapy by simultaneous polytherapy.

MONOTHERAPY VS POLYTHERAPY OF EXPERIMENTAL SE

- LITHIUM (3 Meq/kg)-PILOCARPINE (60 mg/kg) MODEL
- Methylscopolamine to reduce bronchial secretions
- Atropine (10 mg/kg) with treatment to eliminate initial trigger
- Treat when pharmacoresistance is established (after 2d stage ≥ 3 seizure)
- Combine a benzodiazepine GABAA agonist, and NMDA antagonist and an enhancer of inhibition acting at a non-benzodiazepine site
- Compare triple therapy to monotherapy at ≥ triple dose

MONOTHERAPY VS POLYTHERAPY OF SE



MONOTHERAPY VS POLYTHERAPY OF SE

- AT THIS DOSE, VALPROATE HAD NO EFFECT ON RSE
- DIAZEPAM AND KETAMINE HAD A MODEST EFFECT ON RSE
- TRIPLE THERAPY HAD A STRONG EFFECT ON TERMINATION OF RSE ($p < 0.01$)
- PHARMACORESISTANCE WAS GREATLY REDUCED BUT NOT ELIMINATED

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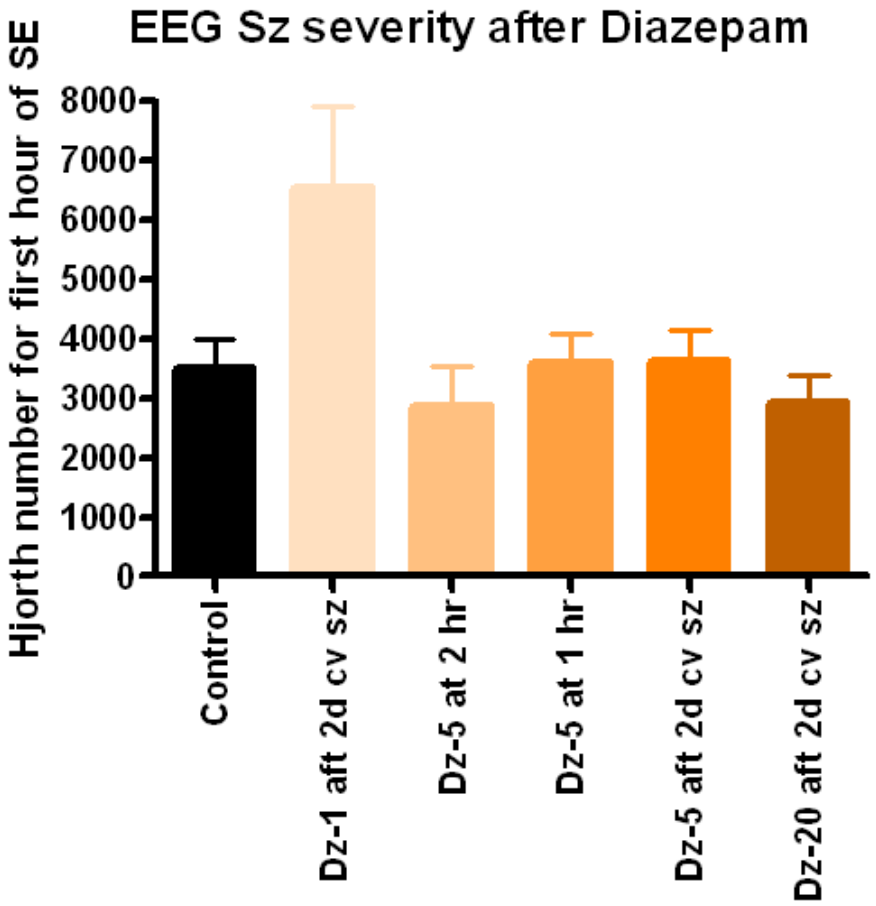
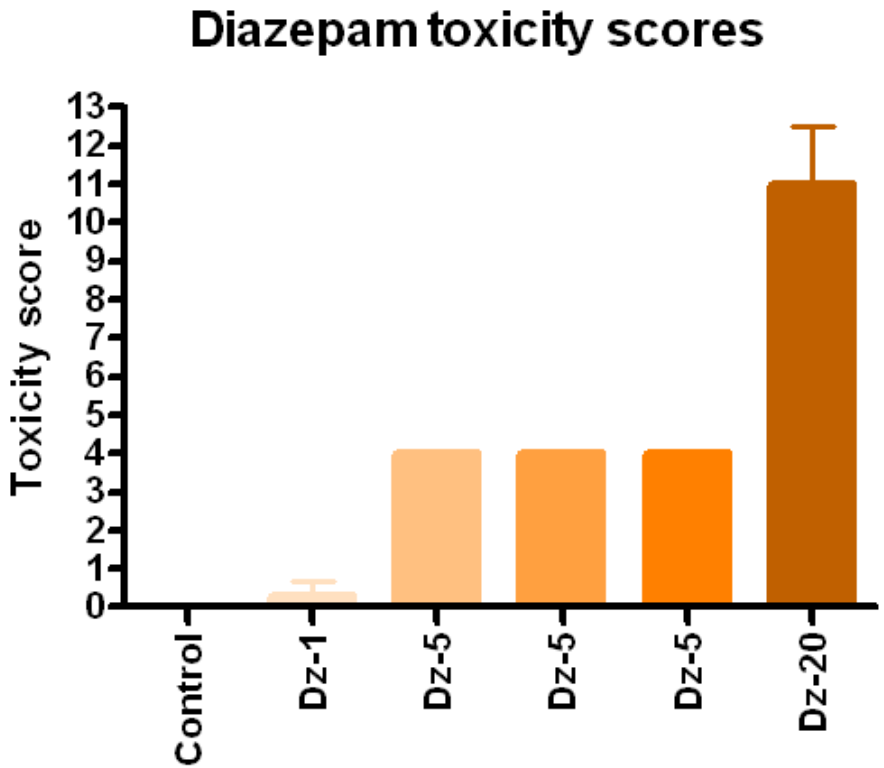
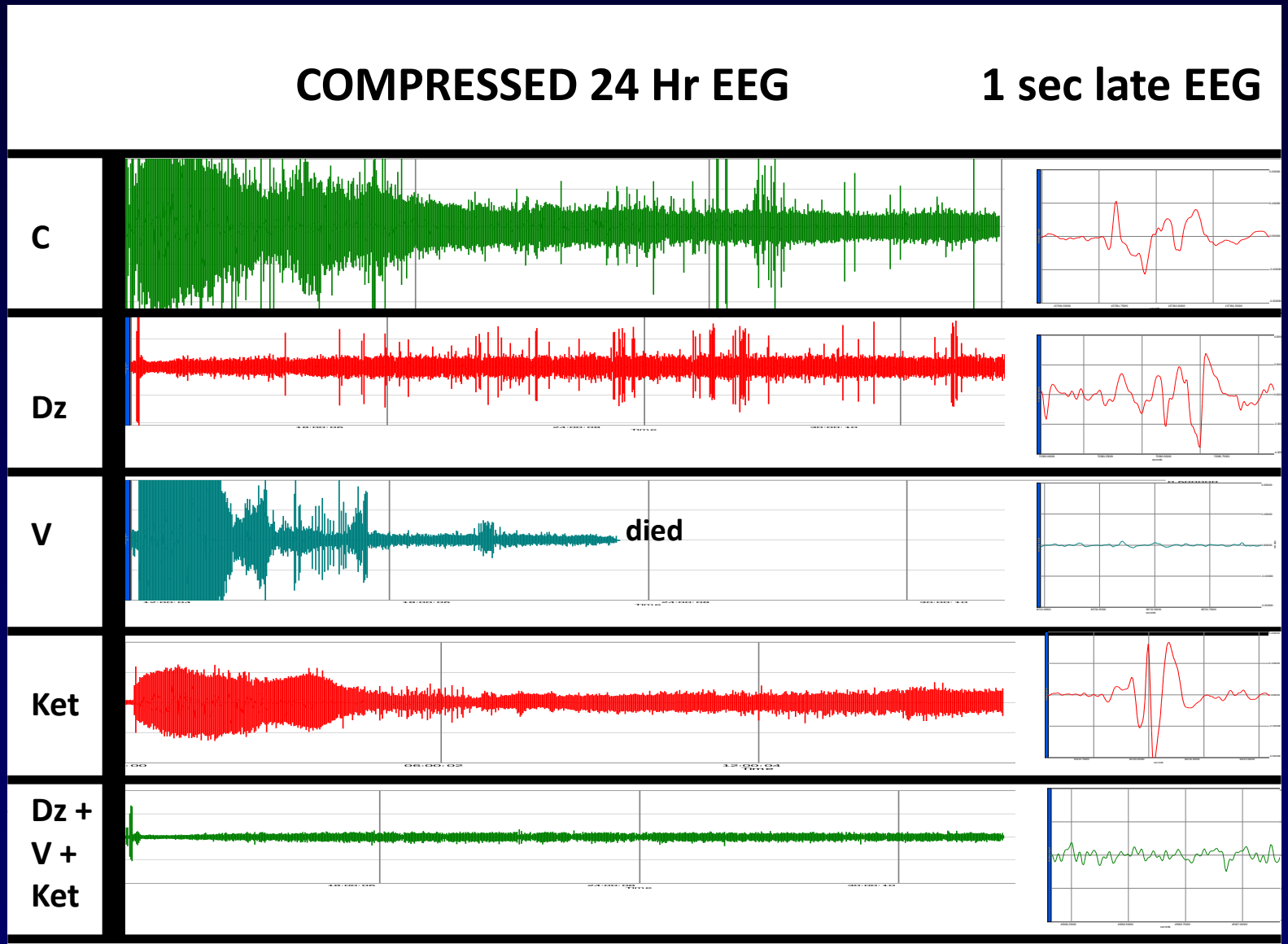
BENZODIAZEPINE PHARMACORESISTANCE DURING SE





MONOTHERAPY VERSUS POLYTHERAPY



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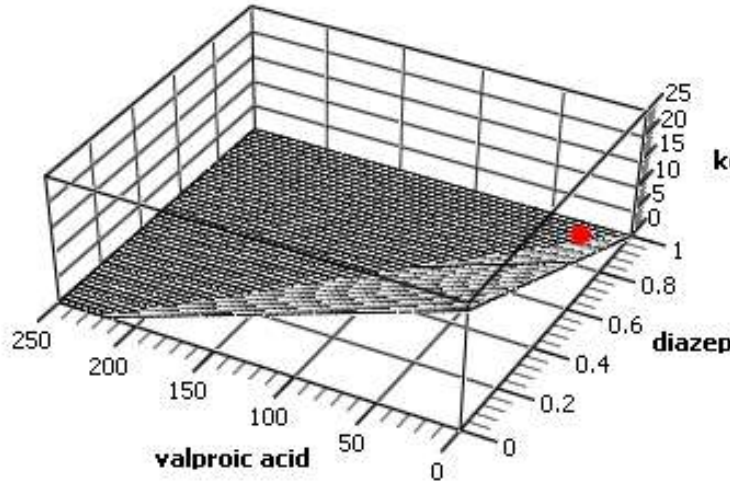
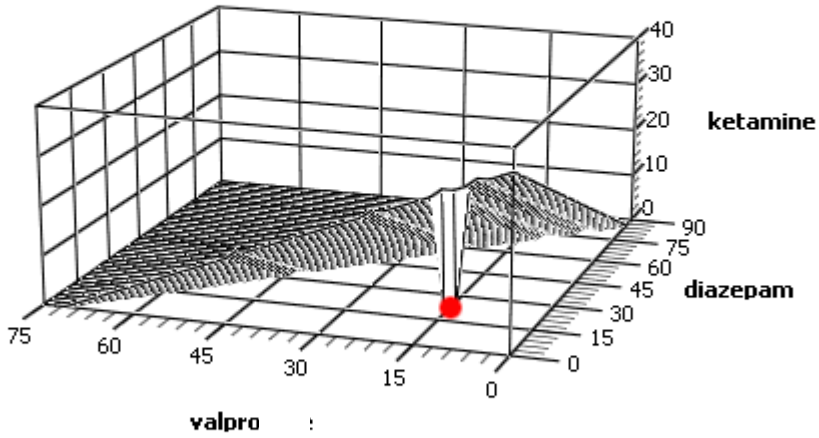
ISOBOLOGRAMS SUGGEST POSITIVE COOPERATIVITY BETWEEN THE THERAPEUTIC, BUT NOT THE TOXIC EFFECTS OF SOME DRUG COMBINATIONS

VALPROATE + DIAZEPAM + KETAMINE

Toxicity score



Reduction of EEG power



MONO- VERSUS POLYTHERAPY IN THE TREATMENT OF STATUS EPILEPTICUS

- The benefits of monotherapy in the treatment of chronic epilepsy may not apply to SE
- Some drug combinations may have synergistic effects
- In SE, it may be beneficial to enhance inhibition AND reduce excitation **from the start**
- Early polytherapy may reduce pharmacoresistance
- Clinical trials of SE should include a polytherapy arm

Our greatest challenge:
How can we translate these animal data into human applications?