

Pathophysiology and Treatment of Refractory SE: Lessons from Animal Models

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Disclosures

Name of Commercial
Interest

NIH (NINDS)

VA Health Administration

Type of Financial
Relationship

Research Grants

Research Grant

FDA Approval

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

Learning Objectives

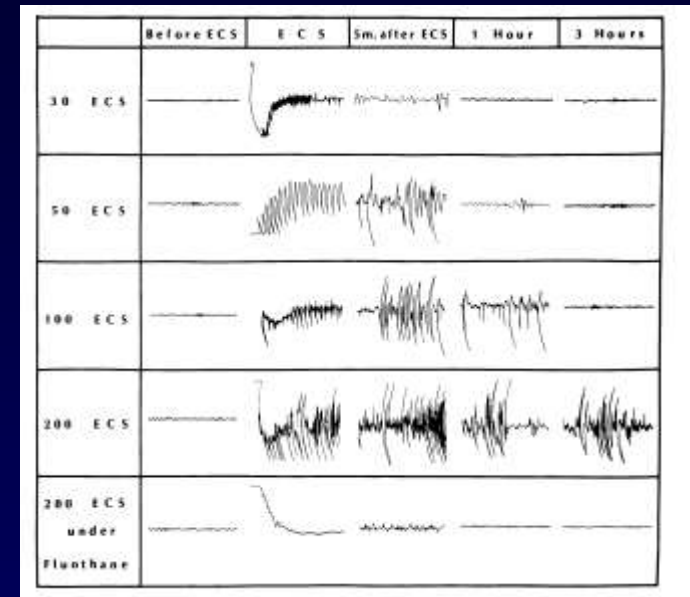
- **Understanding some recent advances in the pathophysiology of status epilepticus**
- **Understanding the therapeutic implications of those basic advances**

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PATHOPHYSIOLOGY OF STATUS EPILEPTICUS

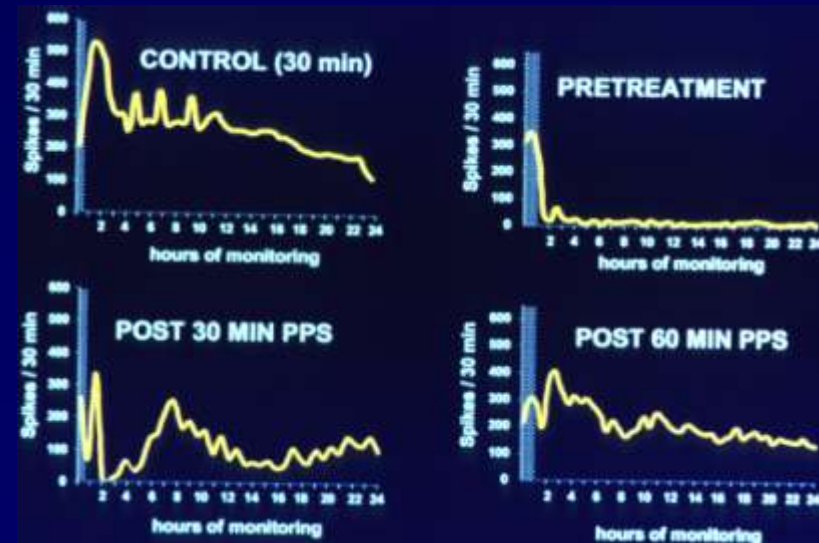
SEIZURES BECOME SELF-SUSTAINING AND INDEPENDENT OF THEIR ORIGINAL TRIGGER

Wasterlain 1974

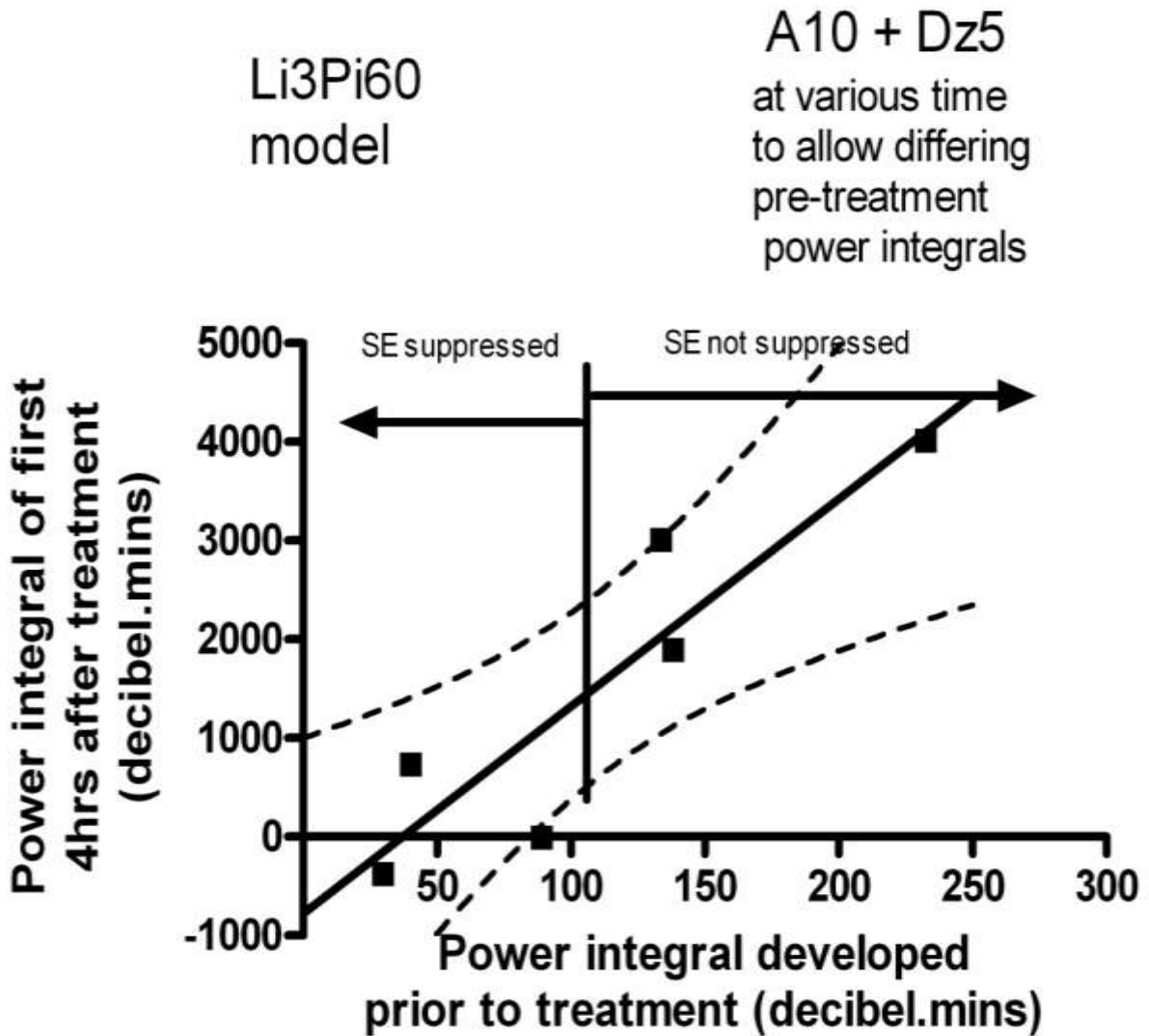


TIME-DEPENDENT DEVELOPMENT OF PHARMACORESISTANCE TO BENZODIAZEPINES (diazepam 5 mg/kg)

Kapur & MacDonald 1997, Mazarati et al 1998

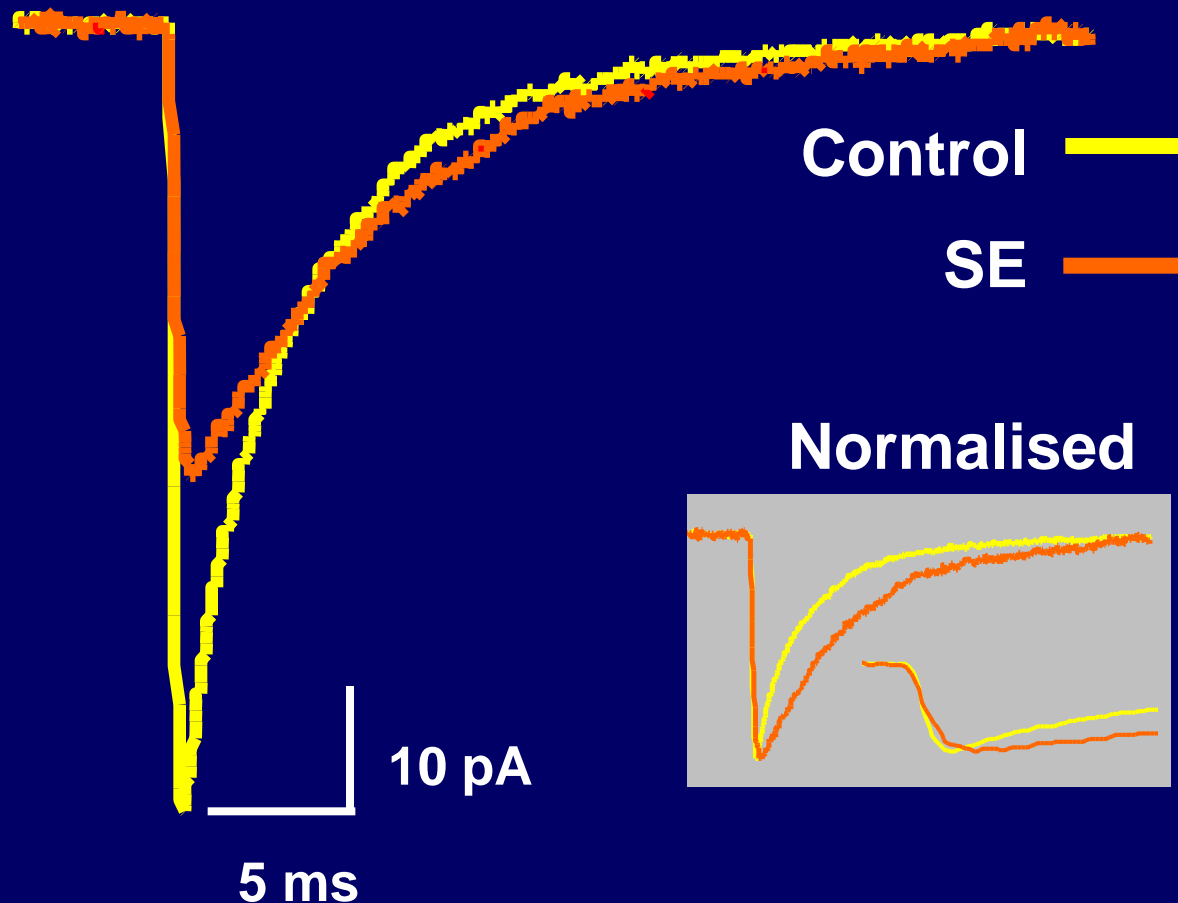


PHARMACORESISTANCE CORRELATES WITH EEG POWER INTEGRAL BEFORE TREATMENT, SUGGESTING THAT IT IS INFLUENCED BY SEIZURE FREQUENCY AND SEVERITY



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

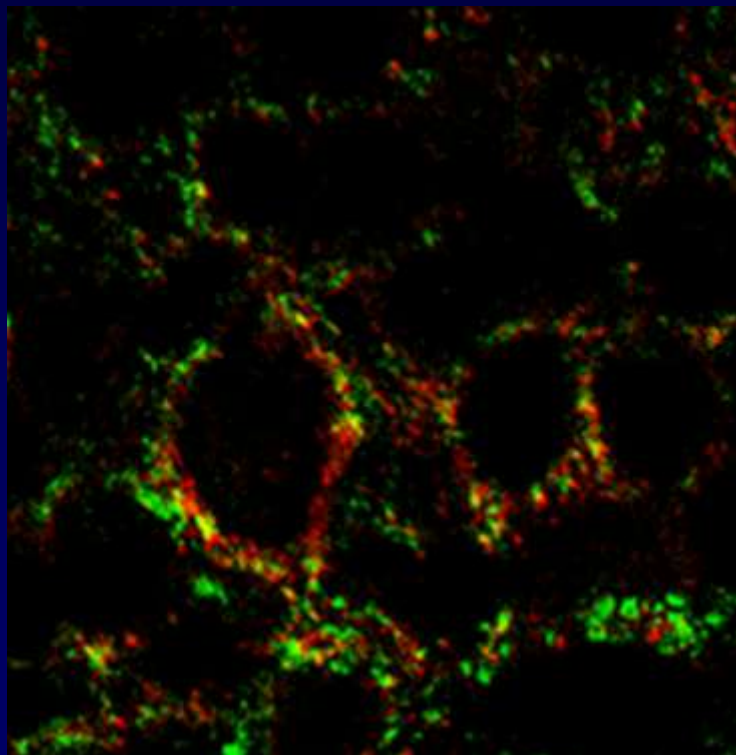
SE: $20 \pm 6^*$

* $p < 0.001$

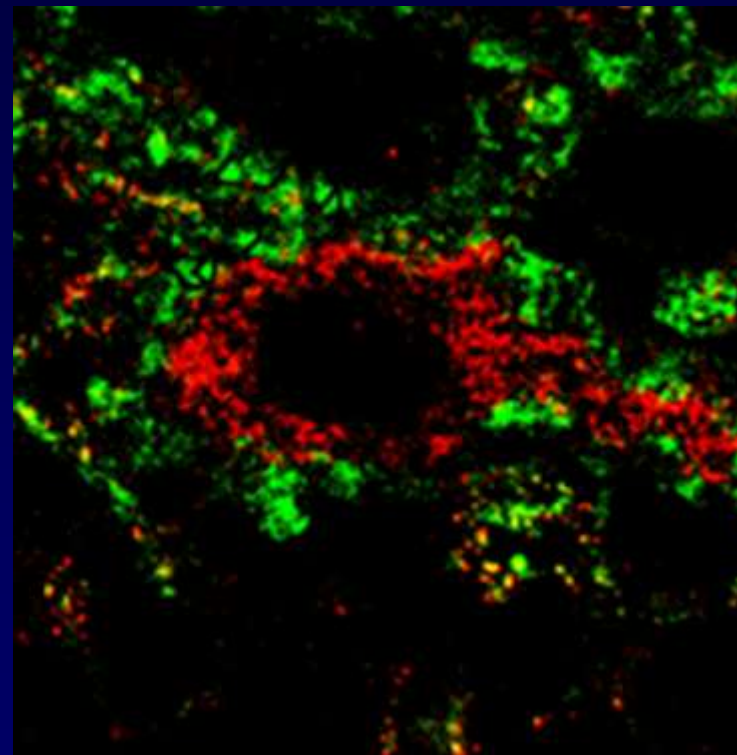
GABA_A receptor trafficking

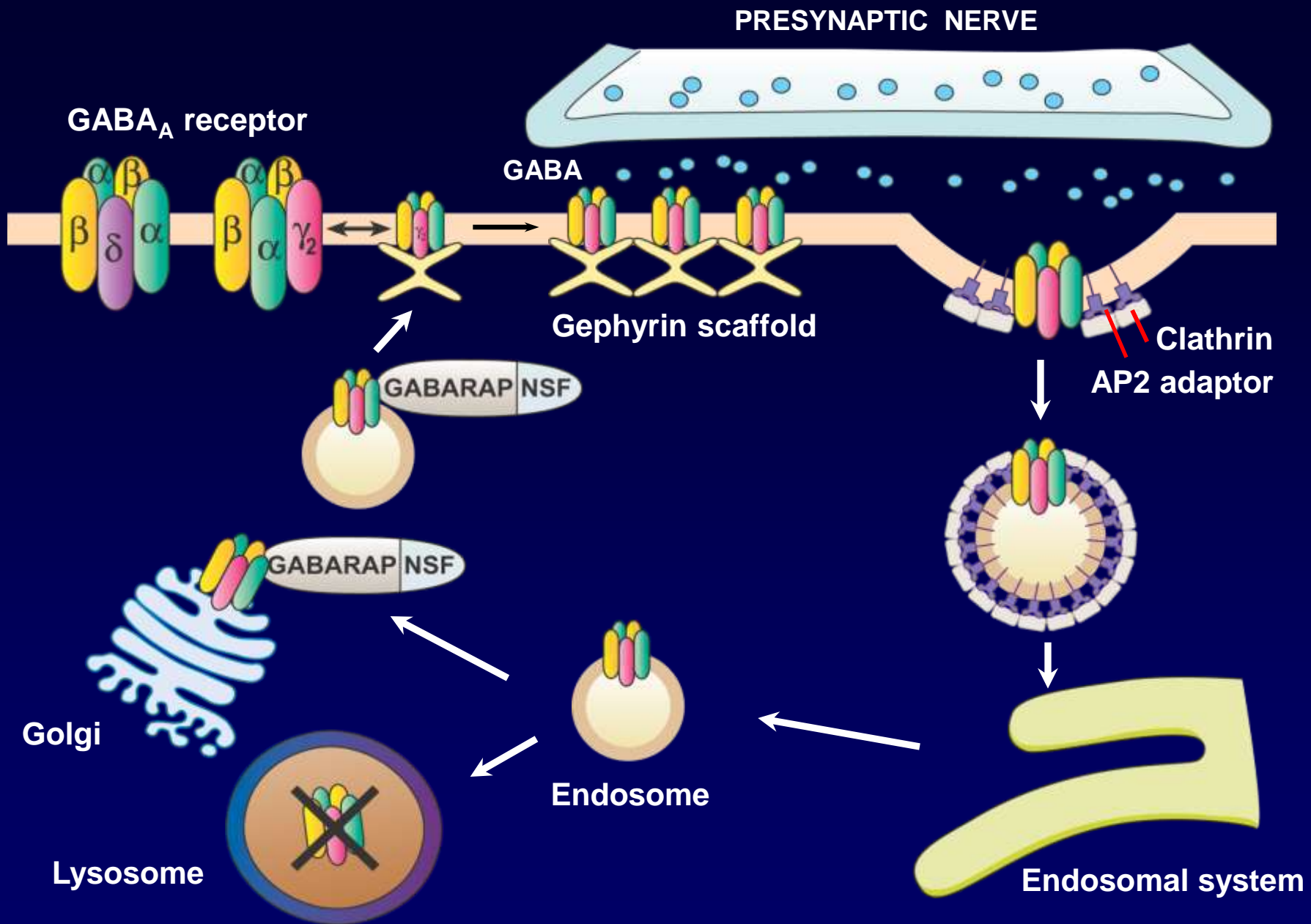
$\beta_{2/3}$ vs synaptophysin

Control

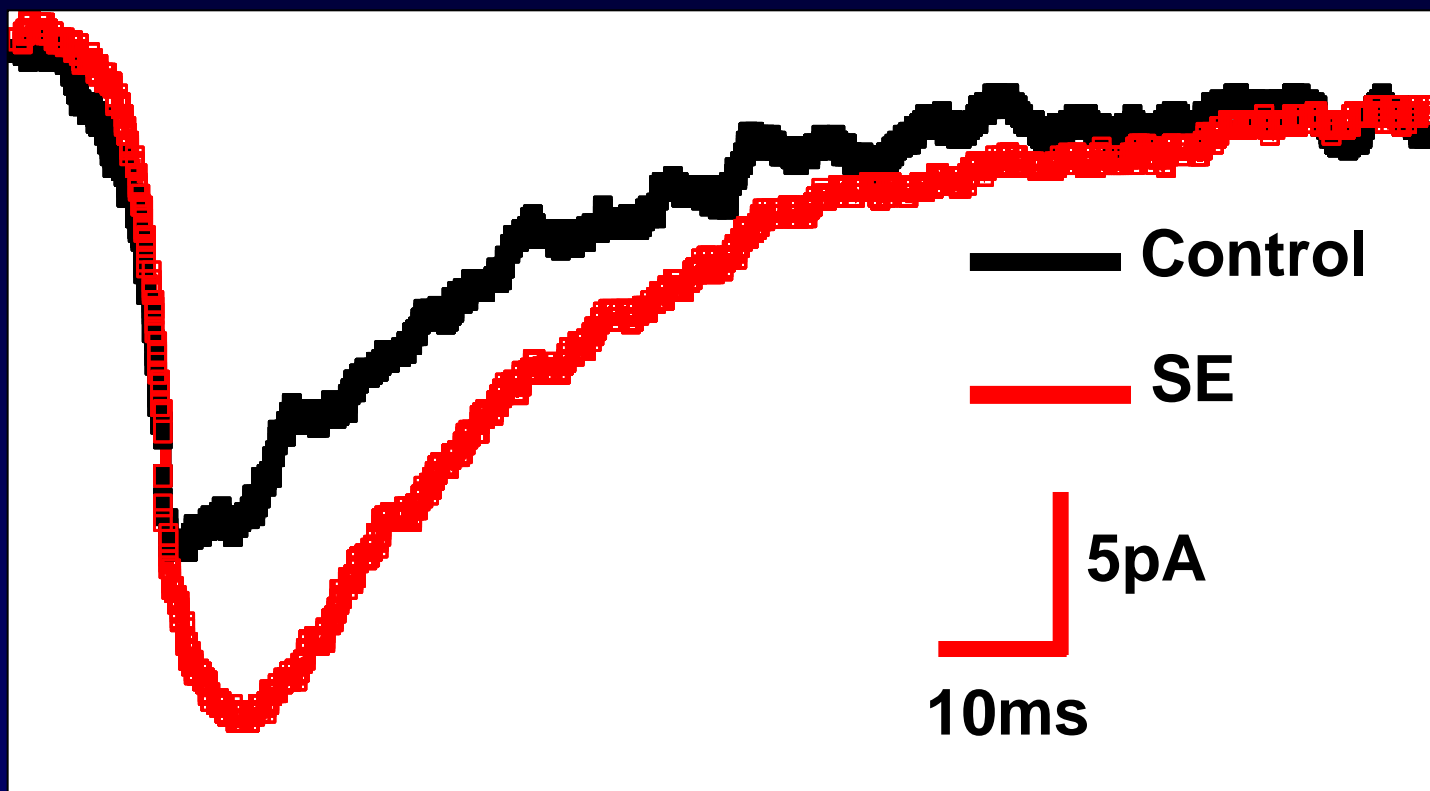


SE



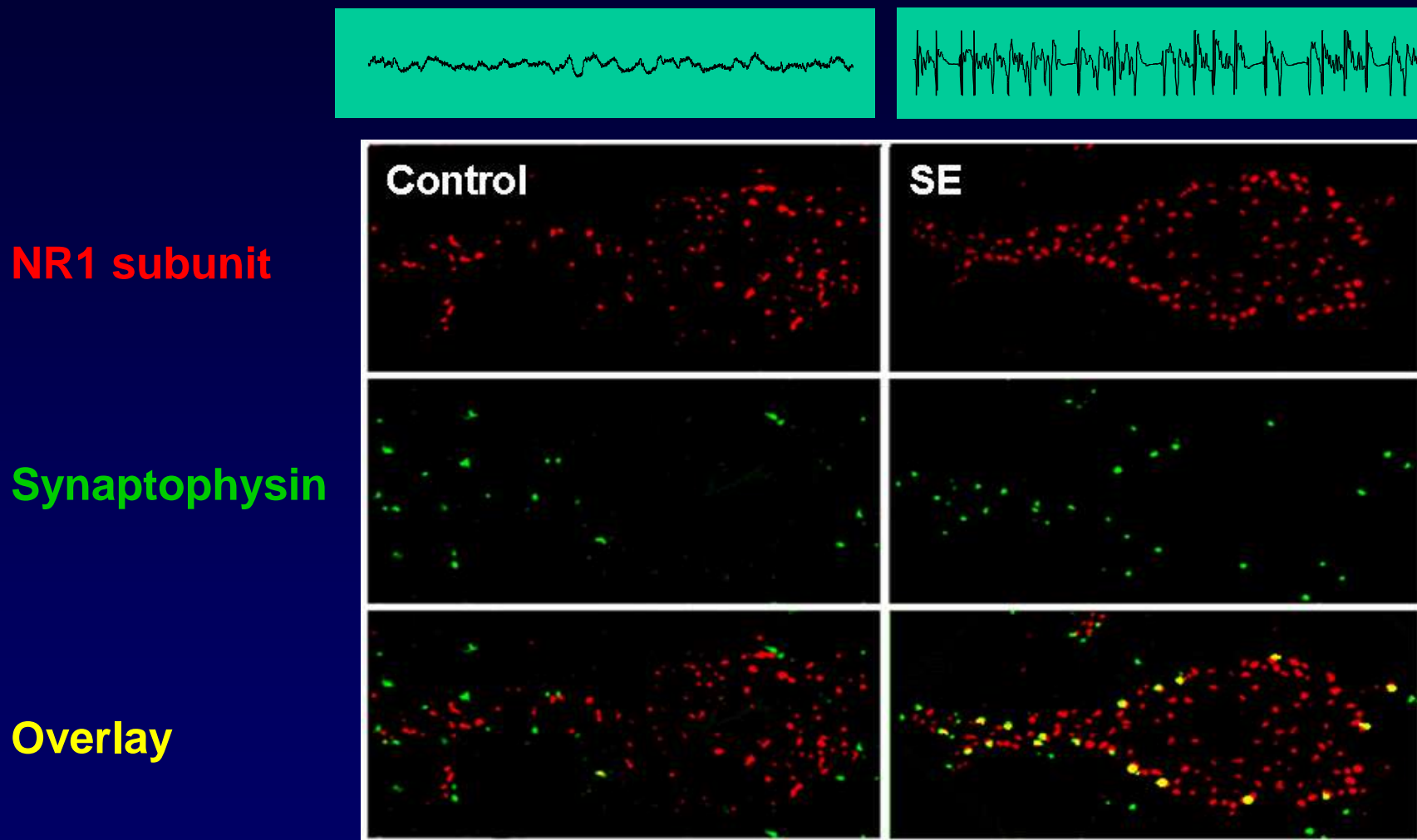


Effect of SE on miniature NMDA EPSCs



Hippocampal slices from 1 hr lithium-pilocarpine SE rats
Number of NMDA receptors / GC synapse: **C** 5 ± 1 , **SE** 8 ± 2 ($p < 0.001$)

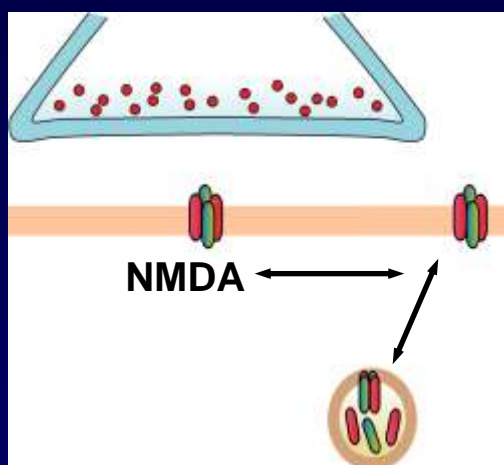
NMDA receptor trafficking during SE



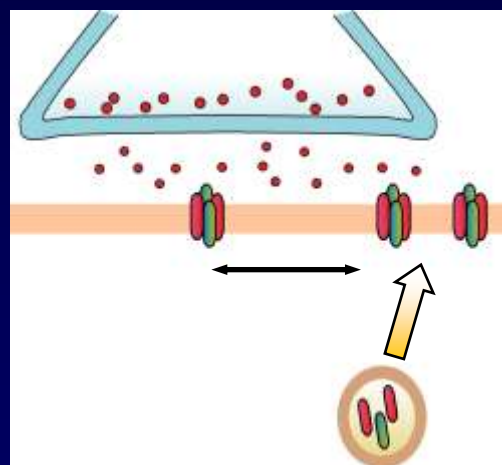
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NMDA synapses

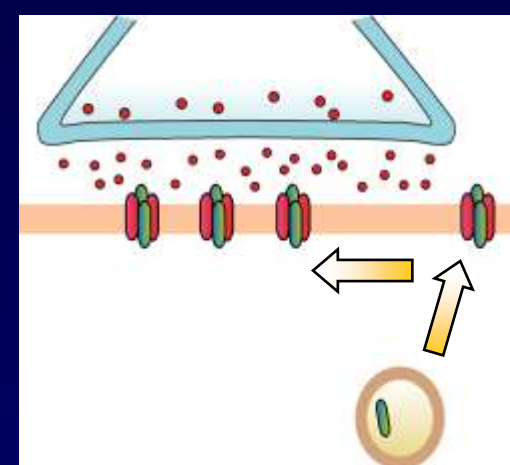
Resting



Stimulation



SE



RECEPTOR TRAFFICKING DURING SE: CAN WE REVERSE ITS CONSEQUENCES?

•REDUCED NUMBER OF SYNAPTIC GABA_A R
BENZODIAZEPINES



PHARMACORESISTANCE TO

•INCREASED NUMBER OF SYNAPTIC NMDAR
SUSTAINING SEIZURES



MAINTAIN SELF-

•**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?**

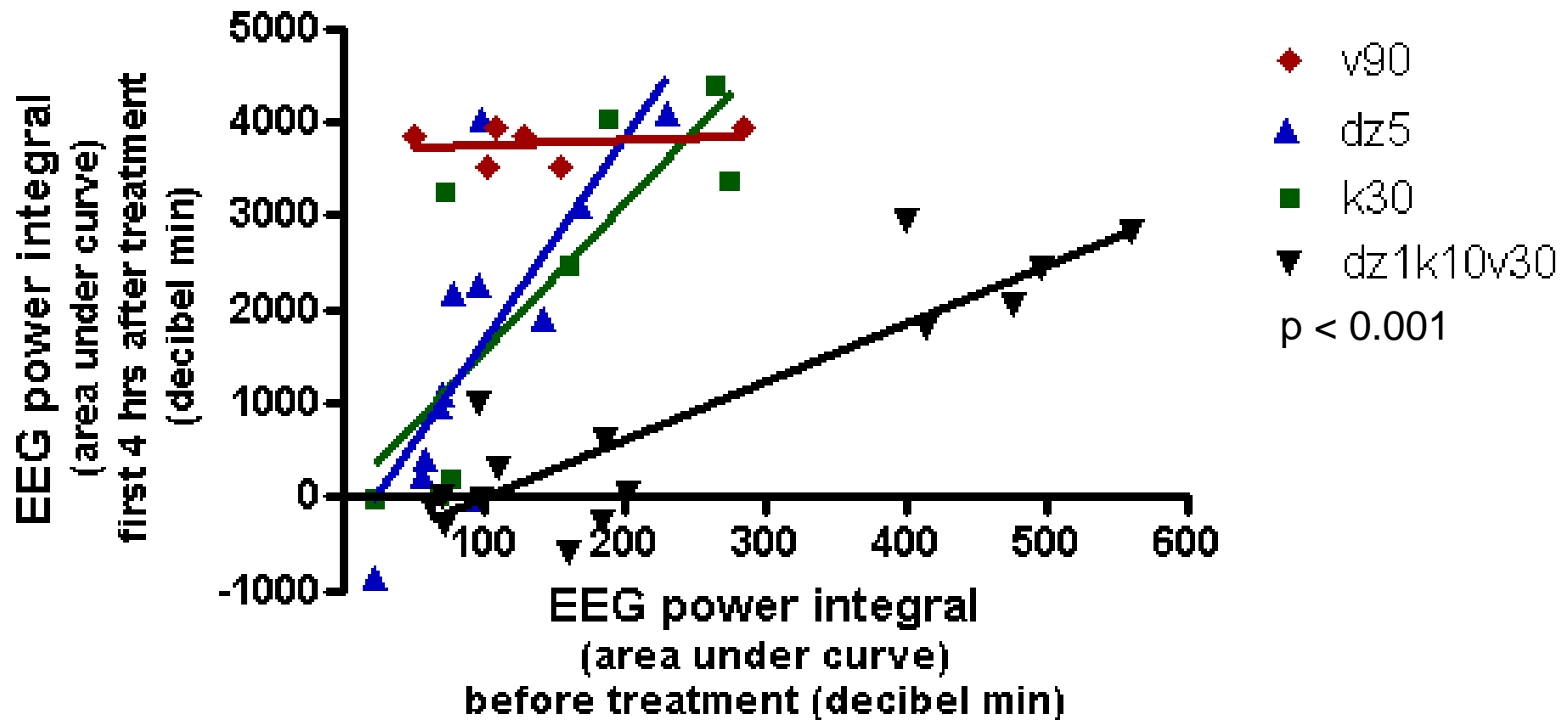
RECEPTOR TRAFFICKING DURING SE: CAN WE USE IT TO SELECT SYNERGISTIC DRUGS?

- 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 \geq 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 \geq triple dose**

MONOTHERAPY VS POLYTHERAPY OF SE



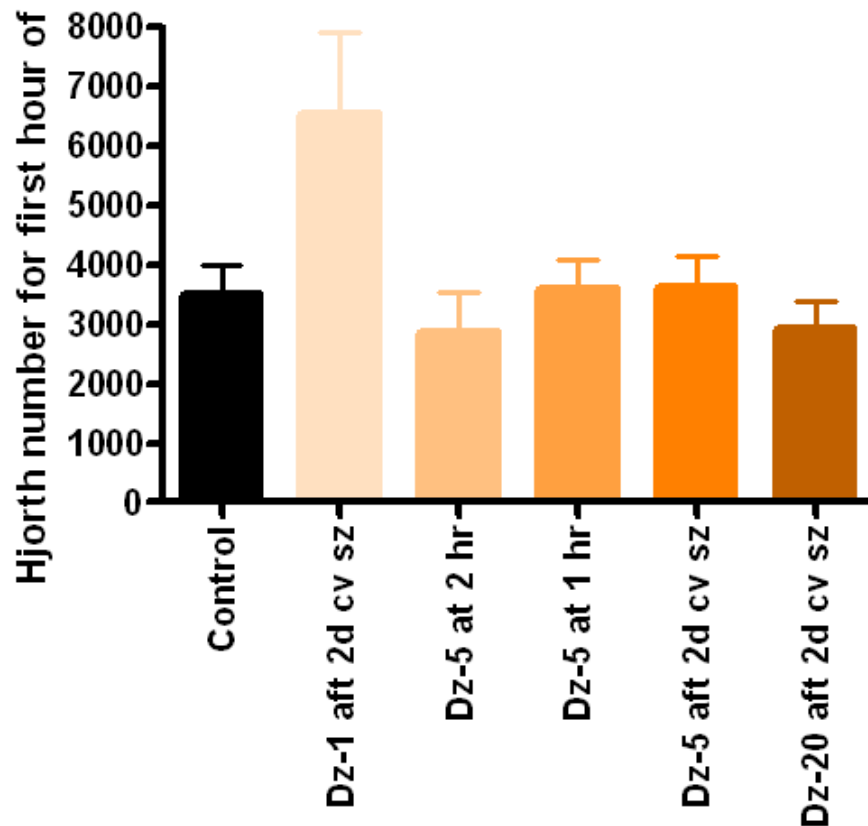
MONOTHERAPY VS POLYTHERAPY OF SE

- 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

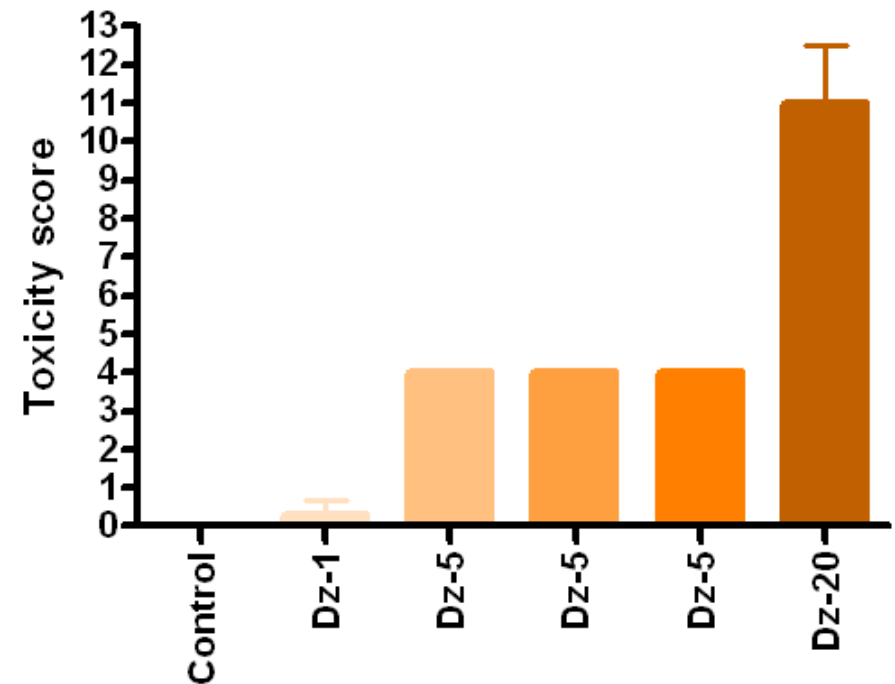
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BENZODIAZEPINE PHARMACORESISTANCE DURING SE

EEG Sz severity after Diazepam



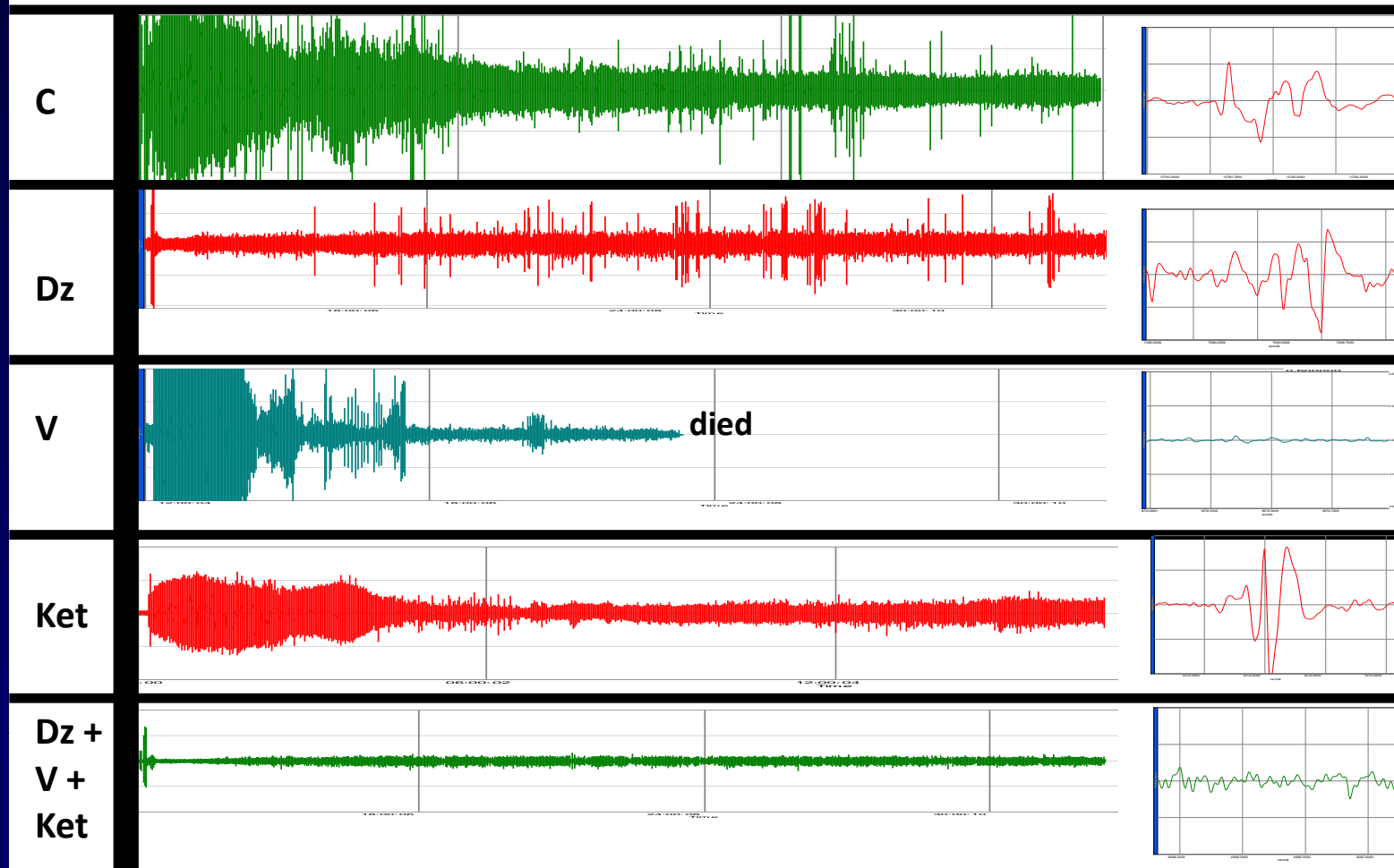
Diazepam toxicity scores



MONOTHERAPY VERSUS POLYTHERAPY

COMPRESSED 24 Hr EEG

1 sec late EEG



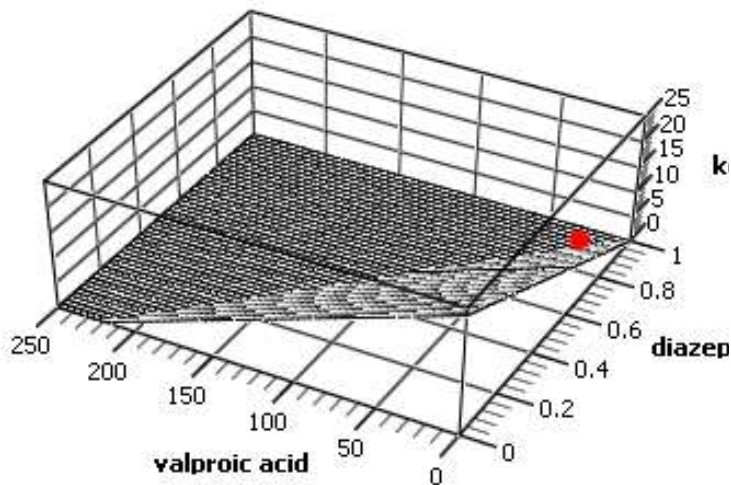
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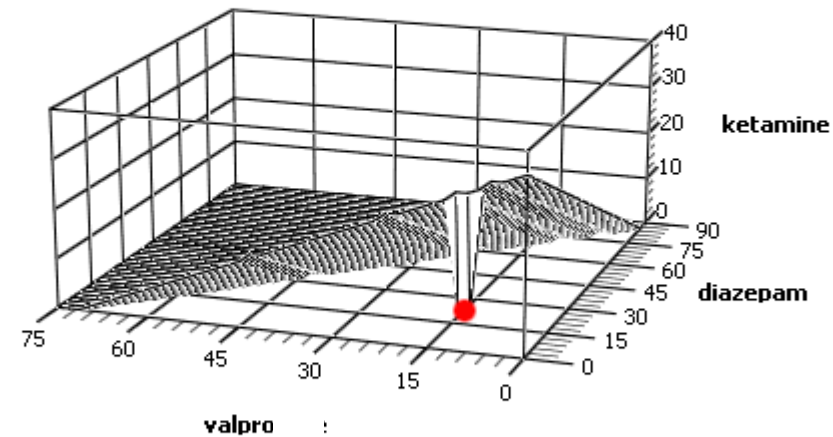
ISOBOLOGRAMS SUGGEST POSITIVE COOPERATIVITY BETWEEN THE THERAPEUTIC, BUT NOT THE TOXIC EFFECTS OF SOME DRUG COMBINATIONS

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?**