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Why can cefepime cause neurological toxicity?

And why is renal failure the main risk factor for this complication?

The answer requires us to learn about cefepime's structure and why it unexpectedly binds to a certain CNS receptor.

#MedTwitter #Tweetorial

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Let's establish a few facts about cefepime:

■4th generation cephalosporin antibiotic
■Excretion = exclusively in the urine (mostly as unchanged drug)
■Readily crosses the blood-brain barrier (so it easily accesses the brain)

https://t.co/rjYG1BfGPR

Cefepime readily crosses the blood-brain barrier

Time after dosing (h)	Cefepime concn (μg/ml)[a]		CSF/plasma ratio
	Plasma	CSF	
0.5	67.1 ± 57.2	5.7 ± 7.3	0.09
1.0	44.1 ± 7.8	4.3 ± 1.5	0.10
2.0	23.9 ± 12.9	3.6 ± 2.0	0.15
4.0	11.7 ± 15.7	4.2 ± 1.1	0.36
8.0	4.9 ± 5.9	3.3 ± 2.8	0.67

[a] Values are means ± standard deviations for five to seven patients at each time point.

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The first report of cefepime neurotoxicity was in 1999.

A patient w/ renal failure received high doses of cefepime and then developed encephalopathy, tremors, myoclonic jerks, and tonic-clonic seizures.

■All symptoms resolved after hemodialysis.

https://t.co/u7JLVitQpp

Cefepime-related neurotoxicity in a haemodialysis patient

Sir,

Our patient was a 40-year-old anuric end-stage renal failure patient on long-term haemodialysis (HD) since 1997. In May 1998, he suffered from an attack of bronchopneumonia with septicaemia. In view of his critical condition, intravenous cefepime at a dose of 1 g every 12 h was started empirically for him. Five days after the commencement of the antibiotic therapy (cumulative dose of 12 g cefepime with one haemodialysis session offered 4 days after cefepime therapy), he became disoriented with waxing and waning mental state followed by an attack of generalized tonic-clonic convulsion. Physical examination showed that he had flapping tremor and generalized myoclonic jerks. His body weight and height

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Cefepime neurotoxicity is surprisingly common, occurring in up to 15% of treated critically ill patients (w/ symptoms varying from encephalopathy to seizures).

■The main risk factors = renal failure and lack of dose adjustment for renal function.

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Table 3 Characteristics of 100 ICU patients receiving intravenous (IV) cefepime

	Cefepime neurotoxicity n = 15	Rest of cohort n = 85	*P* value
Age, years, mean	69	66	0.16
Male gender, n (%)	11 (73)	50 (59)	0.39
Acute kidney injury, n (%)	13 (87)	64 (75)	0.51
Chronic kidney disease, n (%)	10 (67)	30 (35)	**0.042**
Hemodialysis, n (%)	4 (27)	28 (33)	0.77
Peak creatinine, median (IQR)	2.8 (1.7-3.1)*	2.3 (1.5-3)	0.36
Nadir eGFR, median (IQR)	22.5 (20.8-34.3)	27.5 (18-45)	0.53
Mean daily cefepime dose, g, median (IQR)	2.5 (1.7-4)*	2.5 (2-3.5)	0.66
Cefepime duration, days, median (IQR)	5 (4.8-7.3)*	7 (4-10)	0.26
Appropriate dose reduction for renal function, n (%)	4 (29)*	64 (75)	**0.001**

*Data available for 14 of the 15 cases of cefepime neurotoxicity. IQR, interquartile range; g, grams.

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What about cefepime induces neurotoxicity?

One clue is that it's not the only antibiotic that causes neurotoxicity, particularly seizures.

This actually is a class effect w/ other beta-lactam antibiotics (including penicillins and carbapenems).

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Table 2. PROCONVULSANT ACTIVITY OF SELECTED ANTIBIOTICS

Cefonicid	Least seizurogenic
Piperacillin	↓
Cefuroxime	
Azlocillin	
Cefamandole	
Aztreonam	
Ceftezole	
Benzylpenicillin	
Cefazolin	Most seizurogenic

Ranking in potency from least to most seizurogenic after instillation of a 0.1 μMol solution into the cerebral ventricles of rats.

Data from DeSarro A, DeSarro GB, Ascioti C, Nistico G: Epileptic activity of some β-lactam derivatives: Structure activity relationship. Neuropharmacology 28:359–365, 1989.

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Recall that beta-lactam antibiotics all share a common structural feature: a beta-lactam ring.

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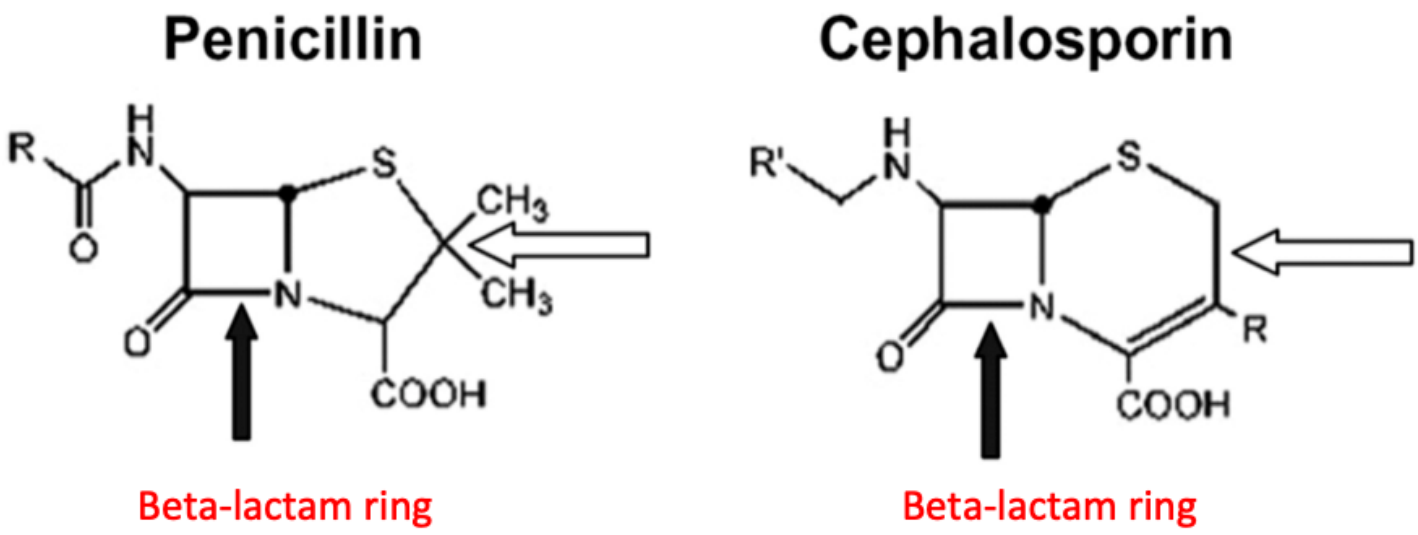

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A 1971 study in cats implicated beta-lactam rings as the source of neurotoxicity.

High doses of penicillin were used to induce seizures.

■But pre-incubation w/ the enzyme beta-lactamase (disrupts the beta-lactam ring) blocked all seizure activity.

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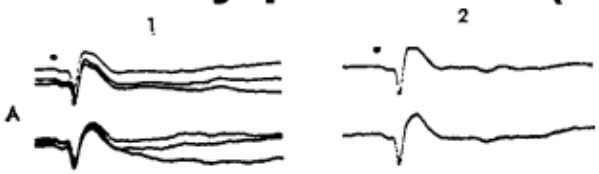
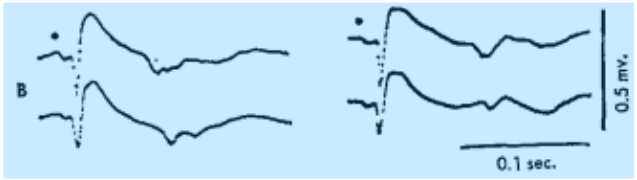
Beta-lactamase prevents seizures induced by penicillin (PCN)



Baseline EEG (Pre-PCN)



Beta-lactamase prevents seizures (Post PCN)

Fig. 2. [A1] Control flash-evoked responses from right (upper trace) and left (lower trace) posterolateral gyri in acue experiment. [A2] Responses twenty minutes after application of penicillinase, 400,000 units per cubic centimeter, to the cortical surface at and around the recording site on the right side. [B1] Control responses to flash recorded from anterior lateral gyri on right (upper trace) and left (lower trace) in the same animal as A. [B2] Responses to same stimuli twenty minutes after application of penicillin-penicillinase mixture to the cortical surface at and around the recording site on the left side. Dots: photic stimuli. Calibrations in B3 for all segments.

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So why can beta-lactam antibiotics like cefepime cause neurotoxicity?

It turns that they block the binding of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) to its receptor.

■Cephalosporins block GABA particularly effectively.

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Cephalosporins block binding of GABA to its receptor (exp in rats)

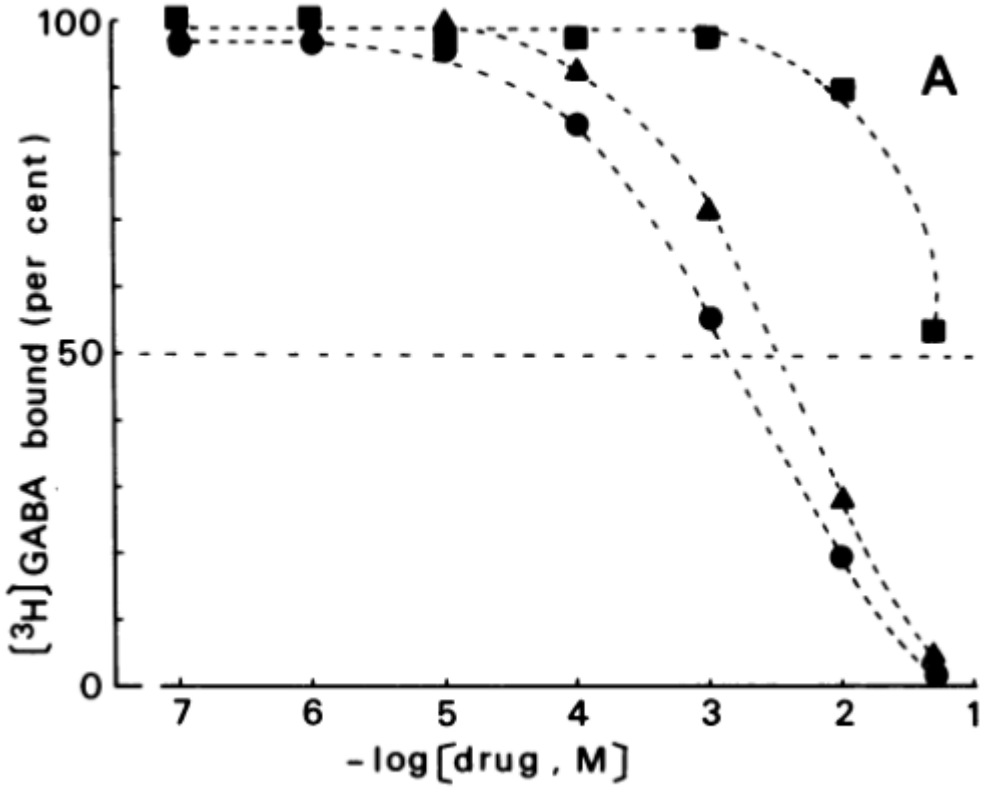

FIG. 1. (A) Effect of cefazolin (●), cephaloridine (▲), and cephalexin (■) on specific ^{3}H-GABA binding in crude synaptic membranes. The binding assay was carried out with 5 nM ^{3}H-GABA.

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The GABA receptor has two subtypes (A and B), and the A subtype functions as a ligand-gated Cl■ ion channel.

Cefepime binds to the GABA-A receptor and blocks Cl■ influx, which correlates with its ability to induce seizure activity.

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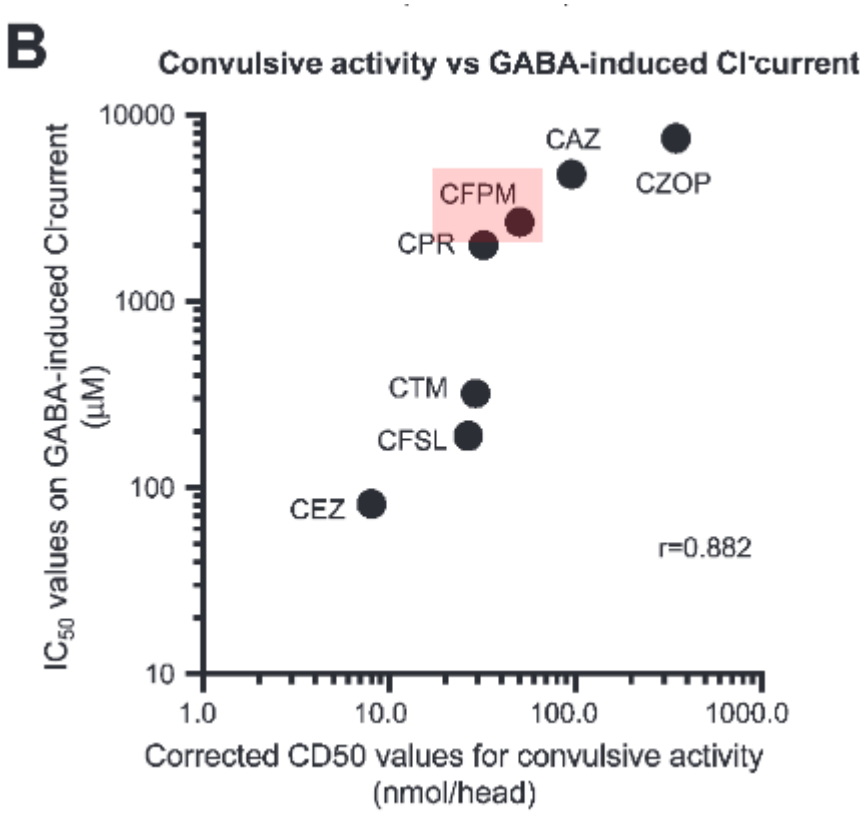

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We've established that cefepime blocks GABA.

This induces neuro-excitation leading to seizures and other neurotoxic manifestations such as tremors and encephalopathy.

■But why is there such a strong link with renal failure?

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An obvious explanation would be that, since cefepime is renally cleared, elevated serum and CNS drug levels build up.

This is supported by the observation that cefepime and other cephalosporins block GABA in a concentration-dependent manner.

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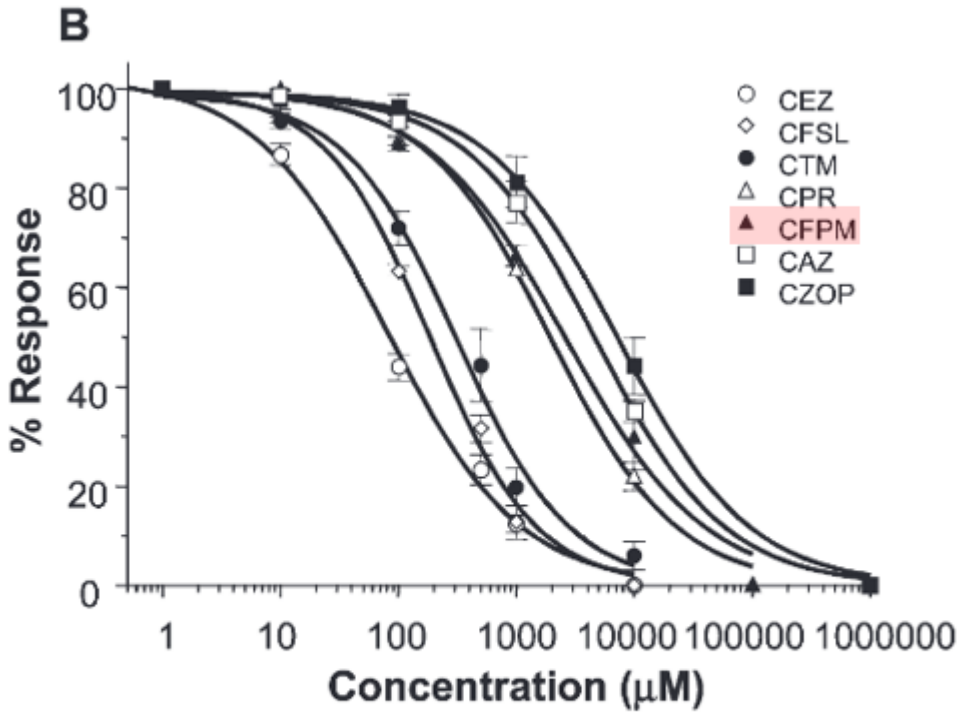

Fig. 3. Cephalosporins inhibit $GABA_A$-R mediated currents. (A) CFSL inhibited GABA (ED_{20})-induced currents in the α1β2γ2s $GABA_A$-R in a concentration-dependent manner.

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But increased drug levels might not be the only reason that patients w/ renal failure are predisposed to neurotoxicity.

The milieu around neurons seems to matter as well.

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This experiment in rat brain slices simulated a "renal" milieu by using a hyperkalemic medium around neurons.

■■Exposure to higher potassium levels significantly increased the ability of cefepime to induce epileptiform discharges.

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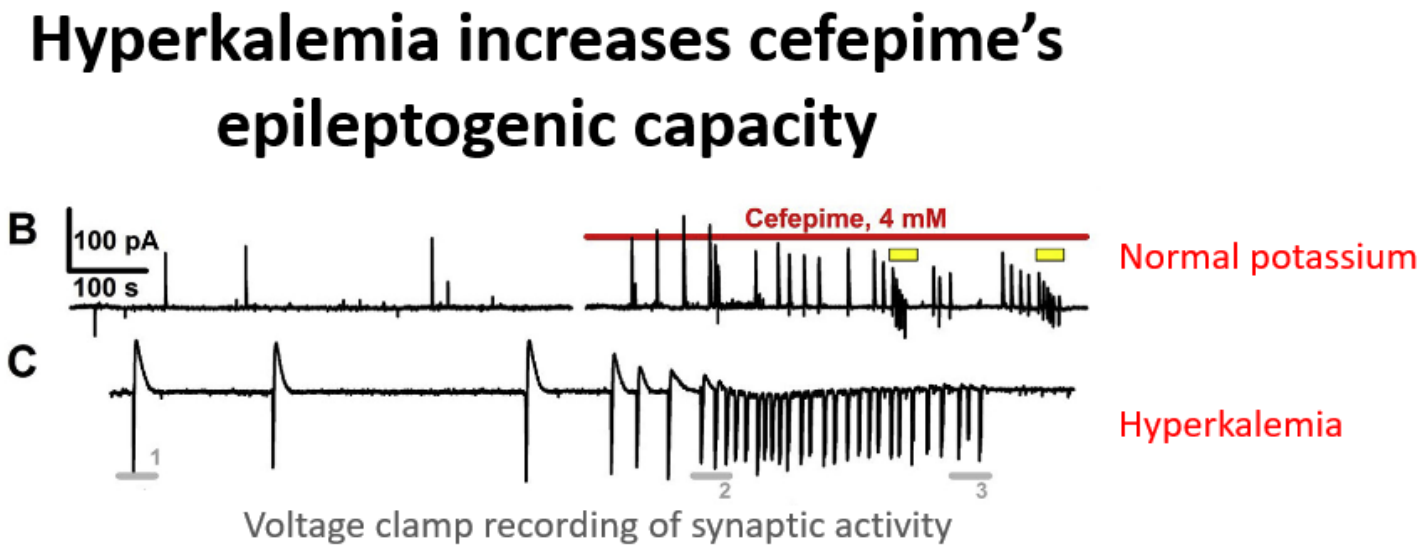

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Let's ask one final question.

Why can cefepime (and other beta-lactam antibiotics) block the GABA receptor?

Exactly why hasn't been well-studied but it likely reflects sufficient structural similarity w/ GABA.

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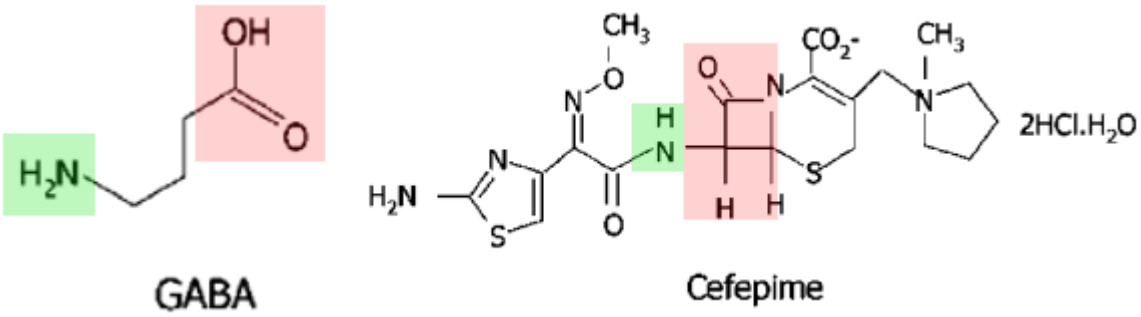

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■Cefepime induces neurotoxicity by blocking the GABA receptor, similar to other beta-lactam antibiotics
■This results from structural similarities between GABA and the beta-lactam ring
■Renal failure = main risk factor b/c of ■■ drug levels +/- hyperkalemia