Why do benzodiazepines act in a time-dependent way?

Even a few minutes of gain in administering rescue benzodiazepines (diazepam, midazolam or lorazepam) can make an immense difference in the outcome of a seizure emergency, as seizures can become refractory if treatment is delayed. This article provides the rationale for why rescue benzodiazepines are more likely to be effective when used earlier on in a seizure emergency.

Seizure Emergency

- In many cases, seizures will stop on their own and do not require a rescue medicine.
- A seizure emergency occurs when a person has a single convulsive seizure or a cluster of convulsive seizures that lasts longer than 5 minutes. In this case, rescue medicines are often given to stop the seizure.
- More information about seizure emergencies can be found here.

GABA receptors (GABARs)

- Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter which works in the brain to reduce the excitability of brain cells (neurons) through its receptors, called GABA receptors (GABARs).
- Rescue benzodiazepines work to stop seizures by activating GABA.
- GABA mediates its inhibitory effects through GABARs which may be synaptic (located in the synapse, or the space between neurons) or extrasynaptic (located outside the synapse).
- Sometimes, GABARs can internalize and become ineffective.
- GABA and GABA receptor interactions are similar to the interactions of your foot and the brake pedal in a car. GABA acts as your foot, which can be used to stop the ‘car’, or in this case, the seizure. GABARs act similar to the brake pedal of a car, acting as the vessel for GABA to stop a seizure. GABA can stop a seizure, or ‘brake the car’, so long as GABARs are still functional, or the ‘brakes of the ‘car’ still remain intact.
    - **If GABARs become ineffective, the ‘brakes’ essentially fail, rendering GABA unable to stop the seizure, much like how your foot cannot stop a car with malfunctioning brakes.**
- In this study, scientists examined changes in GABARs during SE seizures to develop an effective drug to treat SE.
- More information about GABARs in SE can be found here.

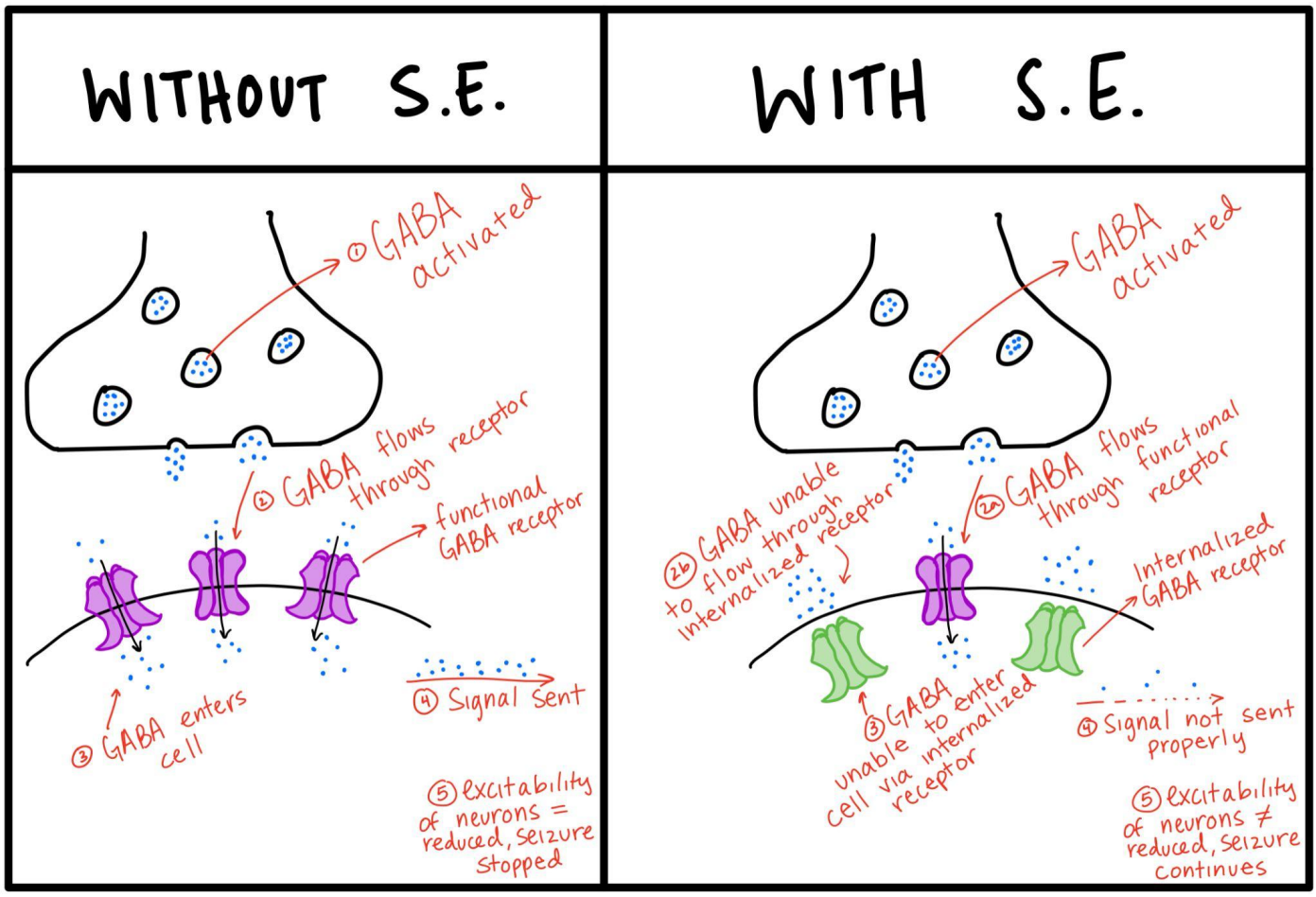

Image on the left (control, without status epilepticus or SE): The inhibitory neurotransmitter GABA flows through GABA receptors, sends a signal to stop the seizure, by reducing the excitability of neurons.

Image on the right (status epilepticus or SE): GABA is unable to flow through the internalized receptor (green), so an inhibitory signal is not sent properly as a result of which, the seizure continues.

Methods

- The experiments described in this paper were done in rats, and care was taken to ensure that the animals did not feel undue pain.
- Rats were administered a chemoconvulsant (a substance that causes seizures), after which brain cells (neurons) in a part of the brain called the hippocampus were examined. The hippocampus was selected due to its role in seizure generation.
- The control group consisted of rats that were not administered the chemoconvulsant, and hence, did not have seizures.
- Electrical and anatomical studies were done to look for changes in brain cells in the hippocampus caused as a result of seizures.

Results

- Prolonged seizures (status epilepticus) led to a reduced number of GABARs – thus GABA could not act on these to reduce the excitability of brain cells.

- These GABARs were internalized (moved inside the cell, as opposed to remaining on the cell surface) and thus GABA could not act on them.
- This loss of GABARs may be a prominent cause in how a single seizure can become a prolonged seizure (status epilepticus), as receptors that have been internalized are not accessible to function normally at the synapses. Additionally, the reduced number of synaptic receptors may explain by rescue benzodiazepines have less effect on stopping seizures, the longer the seizure lasts.
- These discoveries highlight the importance of early treatment for a seizure emergency and that of polytherapy (using multiple drugs) in treating SE. The latter, specifically in cases with delayed treatment times, would allow drugs to only reach the reduced number of GABARs.

Implications for SE treatments

- This study showed that prolonged seizures correlate with a decrease in GABARs, as these receptors are internalized within the cell and are no longer available for GABA to bind to.
    - **Thus, the GABA which normally inhibits excessive brain excitability is unable to act.**
- Intranasal (through the nose) rescue treatments, such as midazolam, or diazepam, have promise due to the rapid absorption rate and the relatively lower difficulty level of administering the drugs.
- Two forms of nasal benzodiazepines - Nayzilam® and Valtoco® were approved by the FDA proving to be examples of how basic science can not only shed light into the mechanisms underlying seizures, but pave the way for therapies as well.

Reference:

Goodkin HP, Joshi S, Mtchedlishvili Z, Brar J, Kapur J. Subunit-specific trafficking of GABA(A) receptors during status epilepticus. J Neurosci. 2008;28(10):2527-2538.

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