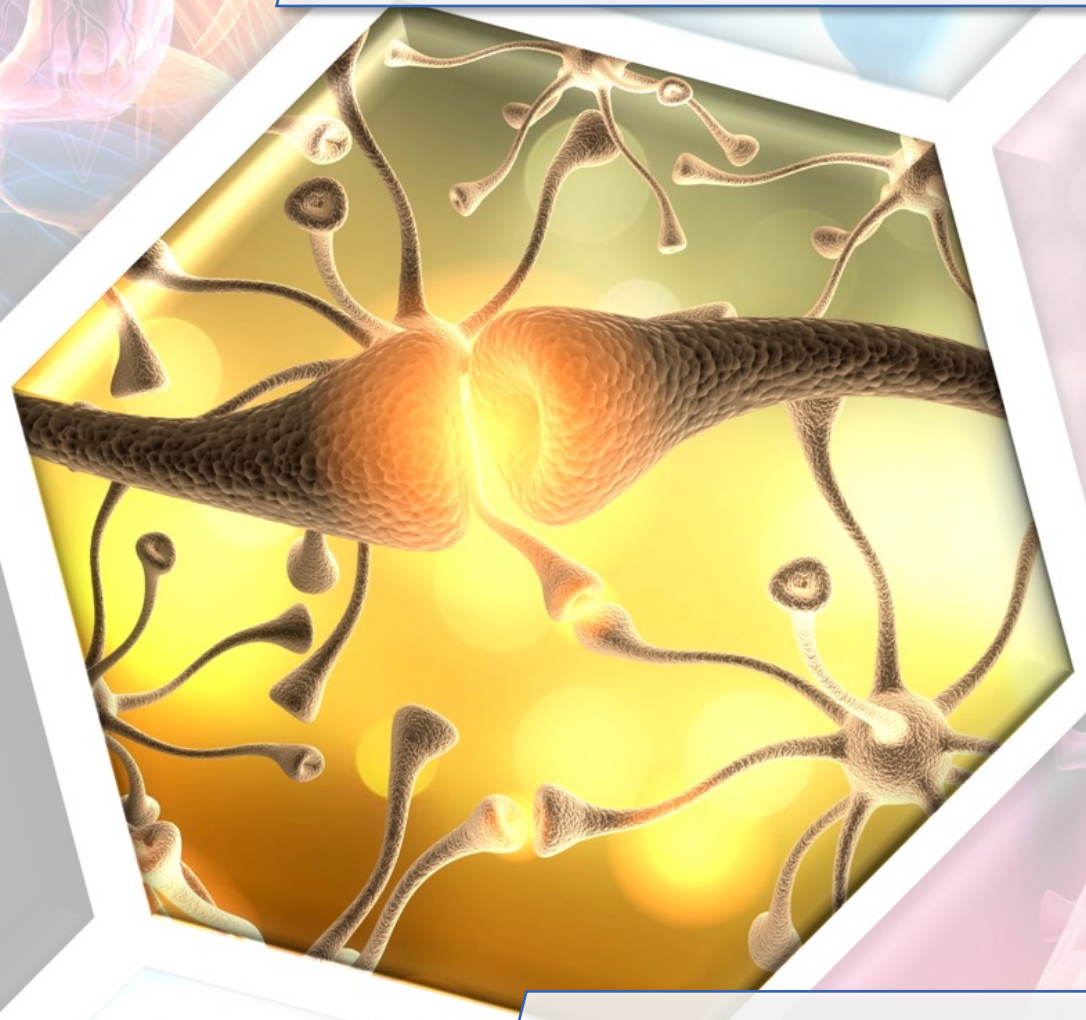
IMPERIAL

# Tutorial – Epilepsy



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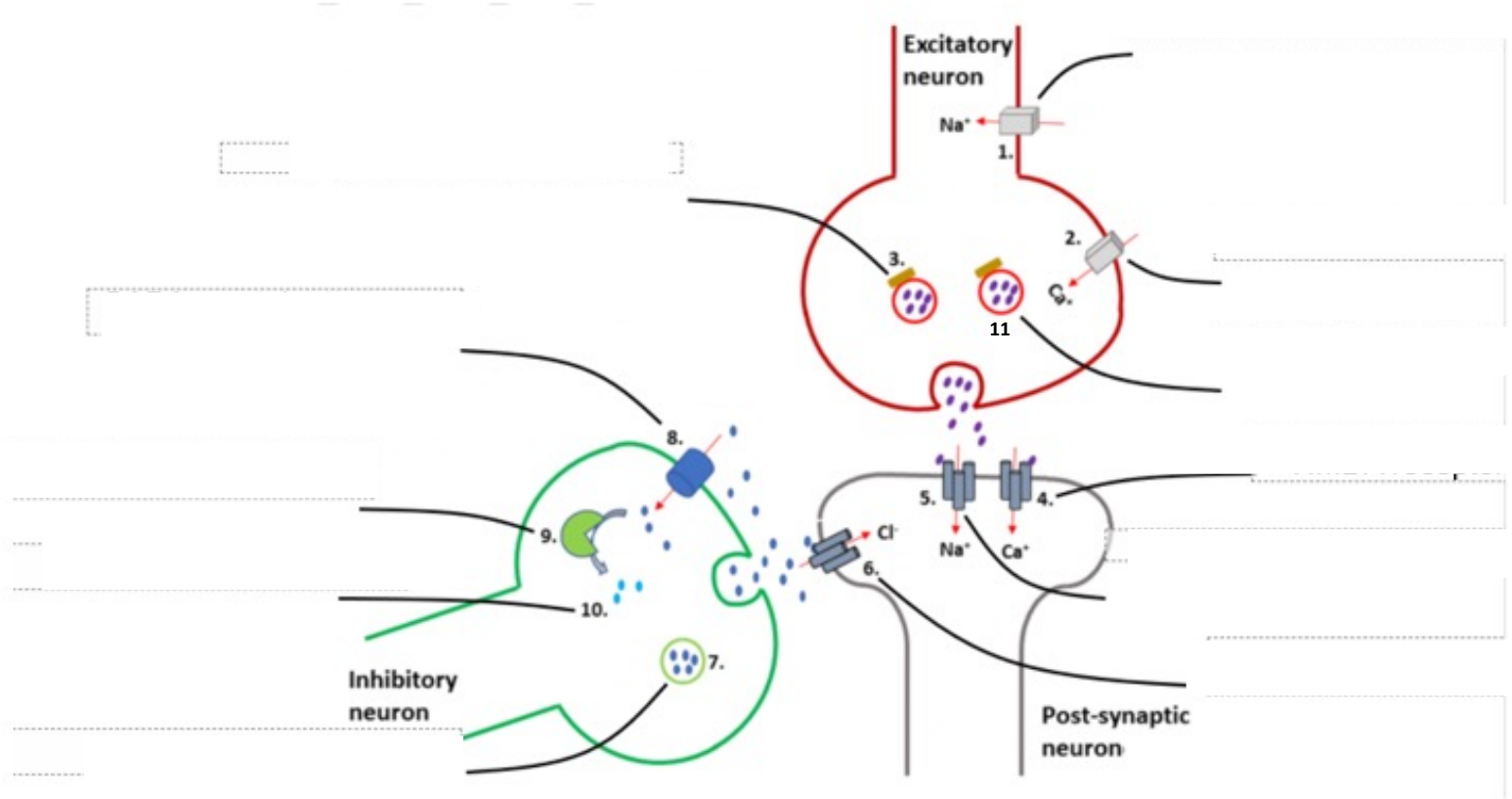
# Part 1A – Introduction to patient case

Miss F (18 years old) presents with several episodes of confusion over the past several months. Typically, she experiences a warning signal, which she describes as a rising sensation within her abdomen that travels upwards through her chest. She is usually unaware for a few minutes, but others have told her that she smacks her lips, picks at her clothing, and is unable to speak during these episodes. After the event she feels tired, has a headache, and prefers to lie down. She notes that her memory has not been as good as it was in the past, and her school grades have declined. Her past medical history is notable for several febrile seizures as a young child – she was treated with diazepam at the time of the seizure but received no ongoing treatment. An aunt was diagnosed with seizures many years ago.

**Miss F is diagnosed with focal (or partial) seizures. The development of seizures is thought to be due to an imbalance between inhibitory and excitatory input within certain brain regions and focal seizures most commonly arise from the temporal lobe.**

# Part 2 – Physiology




The diagram below represents the inhibitory and excitatory input to a post-synaptic neuron in the temporal lobe. Please label the diagram below with the following;

AMPA receptor, $GABA_A$ receptor, GABA reuptake transporter, GABA transaminase, GABA vesicle, glutamate vesicle, NMDA receptor, succinic semi-aldehyde, synaptic vesicle protein, voltage gated sodium channel, voltage gated calcium channel

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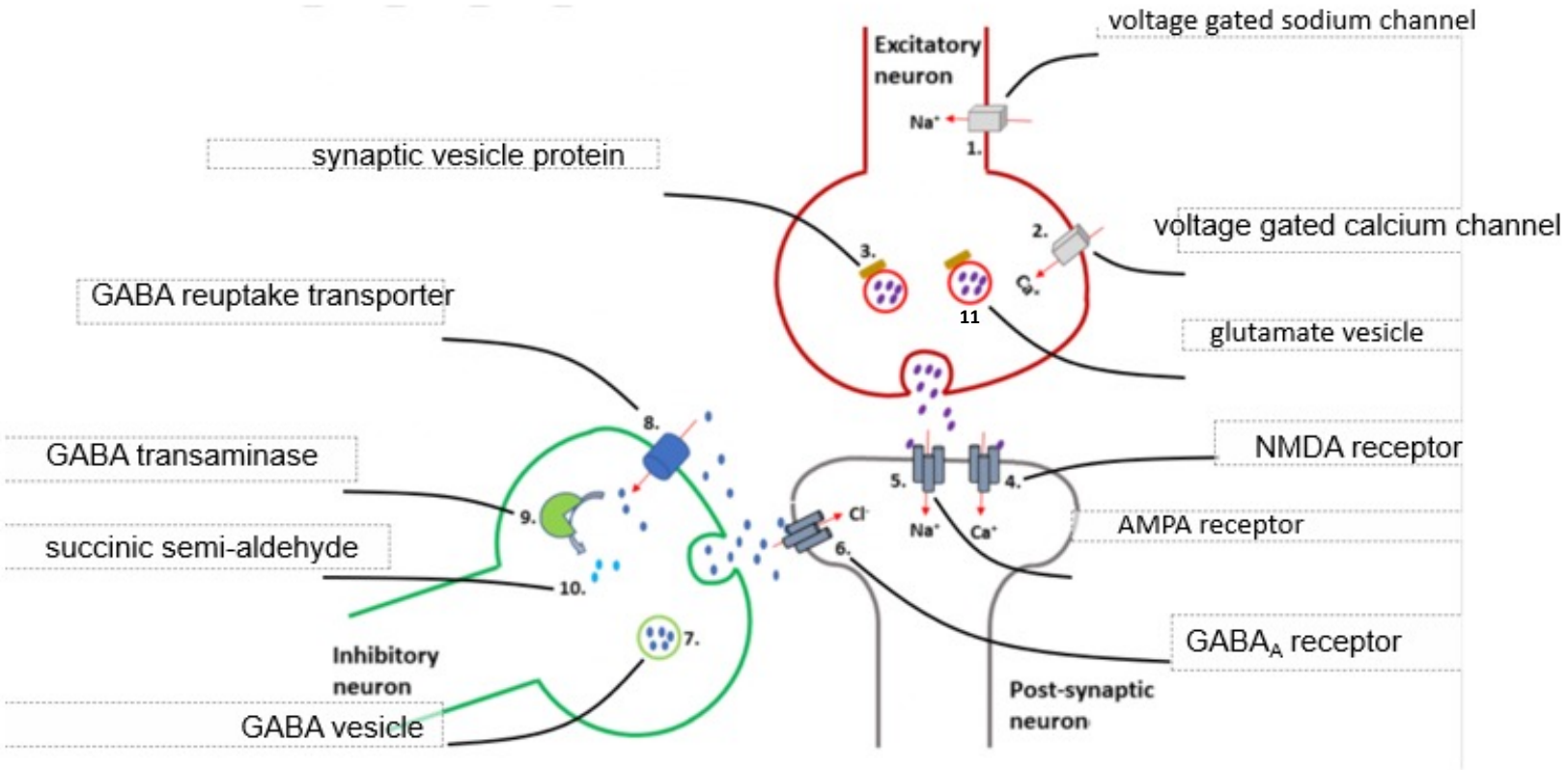


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# Part 3 – Therapeutic options

Q1 of 2. There are four ‘classical’ drug target sites. Can you identify an example for each in the diagram above?

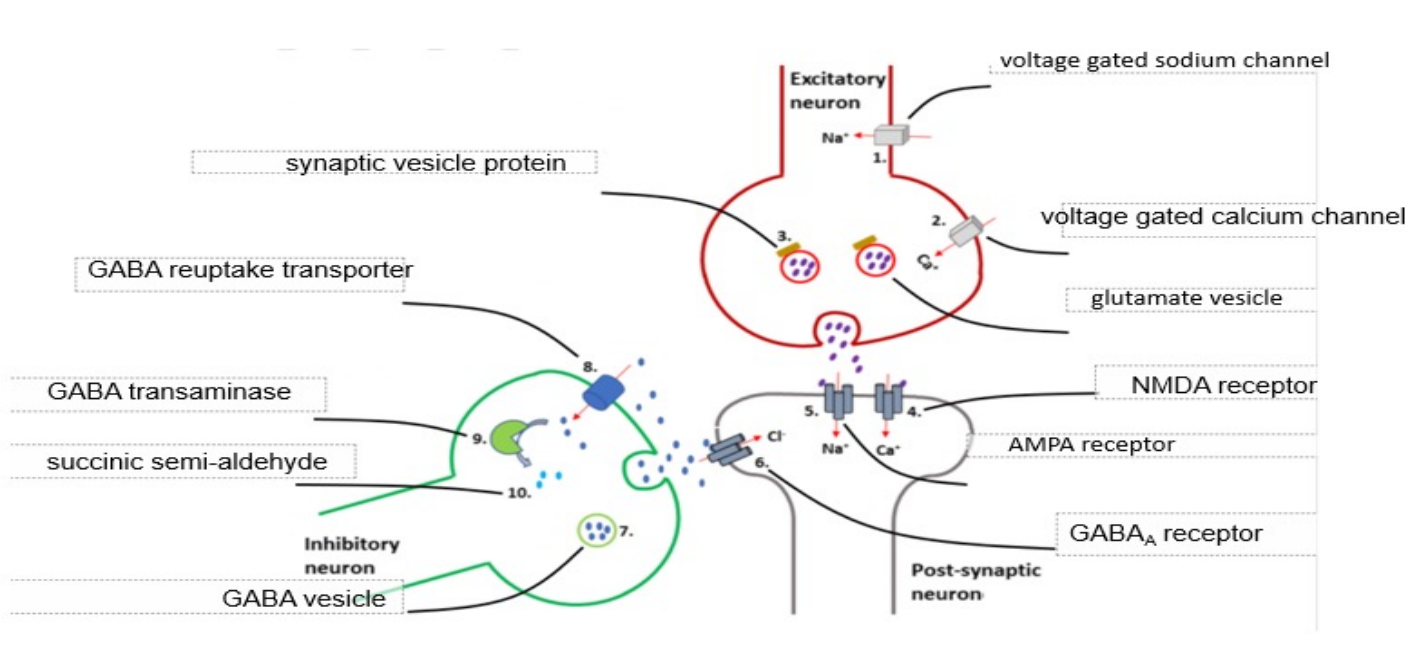
Four classical drug target sites:

1 = Receptors –

2 = Enzymes –

3 = Ion channels –

4 = Transport proteins -



# Part 3 – Therapeutic options

Q1 of 2. There are four ‘classical’ drug target sites. Can you identify an example for each in the diagram above?

Four classical drug target sites:

1 = Receptors – Examples *GABAA receptor,*
*AMPA receptor,*
*NMDA receptor*

2 = Enzymes –Example *GABA transaminase*

3 = Ion channels –Examples *Voltage gated sodium and calcium channel.*

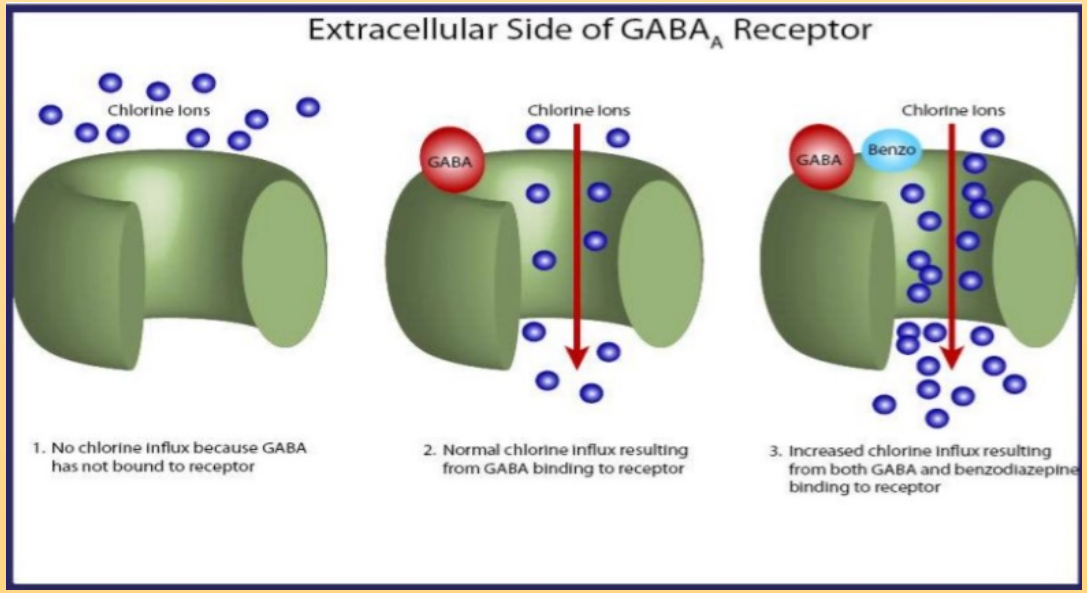
4 = Transport proteins - Example *GABA transporter*

# Part 3 – Therapeutic options

Q2 of 2. As a child, Miss F was treated with diazepam for febrile seizures. What is the drug target for diazepam and how would this help treat the seizures?

What is the drug target?

$GABA_A$ receptor (alpha subunit)




NB – Where is the drug target?

Post-synaptic neurones in the temporal lobe (for complex, partial focal seizures)

What is the result (i.e. how would this help?

*End result – Diazepam binds and increases the effectiveness of GABA activation of this receptor (it doesn't activate the receptor itself). This leads to chloride ion influx (in the presence of GABA) which would hyperpolarize the temporal lobe neurone and decrease the effects observed in the abstract.*

# Part 3 – Therapeutic options

6 months later, Miss F returns to see the consultant neurologist. In the last six months, she has tried the following anti-epileptic drugs. Lamotrigine – which she stopped when she developed a rash and pregabalin – which she didn't like taking because it made her feel nauseous. The neurologist prescribes a different anti-epileptic drug, levetiracetam, for her to try next.

Q. The drug targets for lamotrigine and pregabalin are shown below. How would these drugs act at these targets to produce an anti-epileptic effect?
Lamotrigine – Voltage gated sodium channel
Pregabalin – Voltage gated calcium channel

# Part 3 – Therapeutic options

Q. The drug targets for lamotrigine and pregabalin are shown below. How would these drugs act at these targets to produce an anti-epileptic effect?
Lamotrigine – Voltage gated sodium channel
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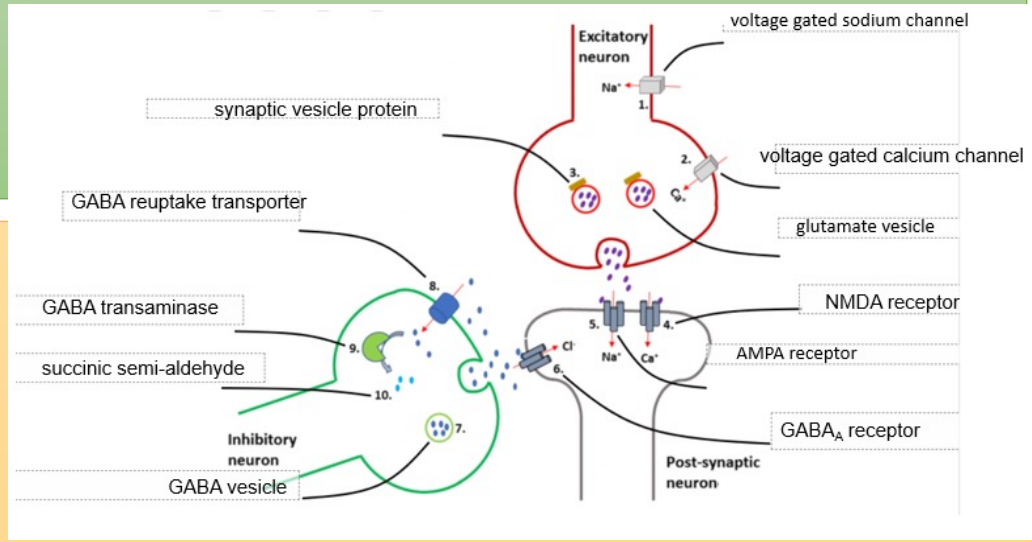



Where is the drug target?
Glutamatergic neurones in the temporal lobe

How do they cause an anti-epileptic effect?
*End result*
*Lamotrigine - Blocking the sodium channels reduces neuronal depolaristion which would eventually lead to neurotransmitter release. In this case, glutamate neurotransmission is decreased and there is less excitatory stimulation of the post-synaptic neurone.*
*Pregabalin - Blocking the calcium channels prevents calcium influx into the neurone which is required to promote vesicle exocytosis and neurotransmitter release. In this case, glutamate neurotransmission is decreased and there is less excitatory stimulation of the post-synaptic neurone.*

# Part 3 – Therapeutic options

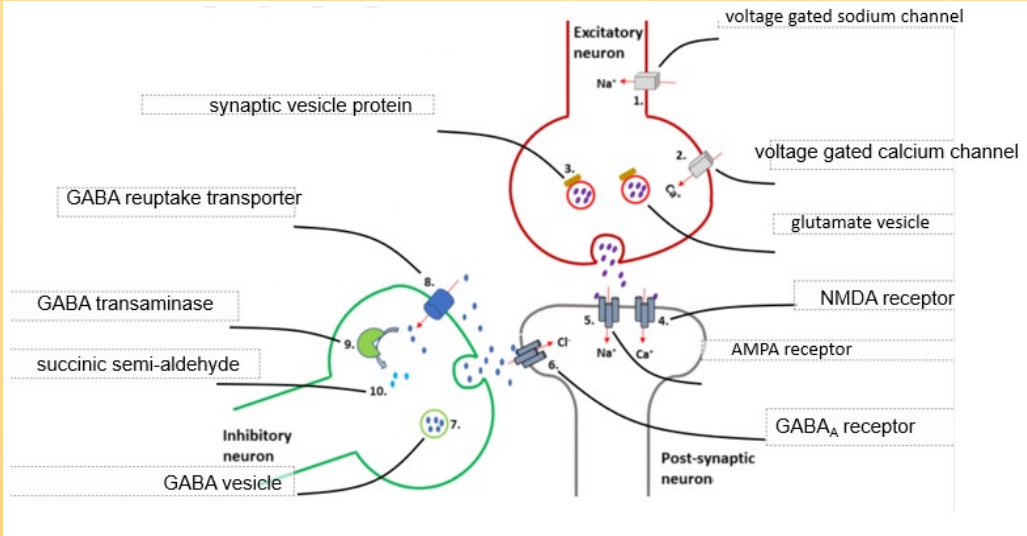
Q. Levetiracetam does not act at one of the classical drug targets. Can you identify the drug target for levetiracetam in the diagram above and explain how the anti-epileptic effect of this drug is produced? [Tip: it also works by reducing glutamate release]

What is the drug target?

*Synaptic vesicle protein SV2A.*

Where is the drug target?

Glutamatergic neurones in the temporal lobe




How do they cause an anti-epileptic effect?

*End result*

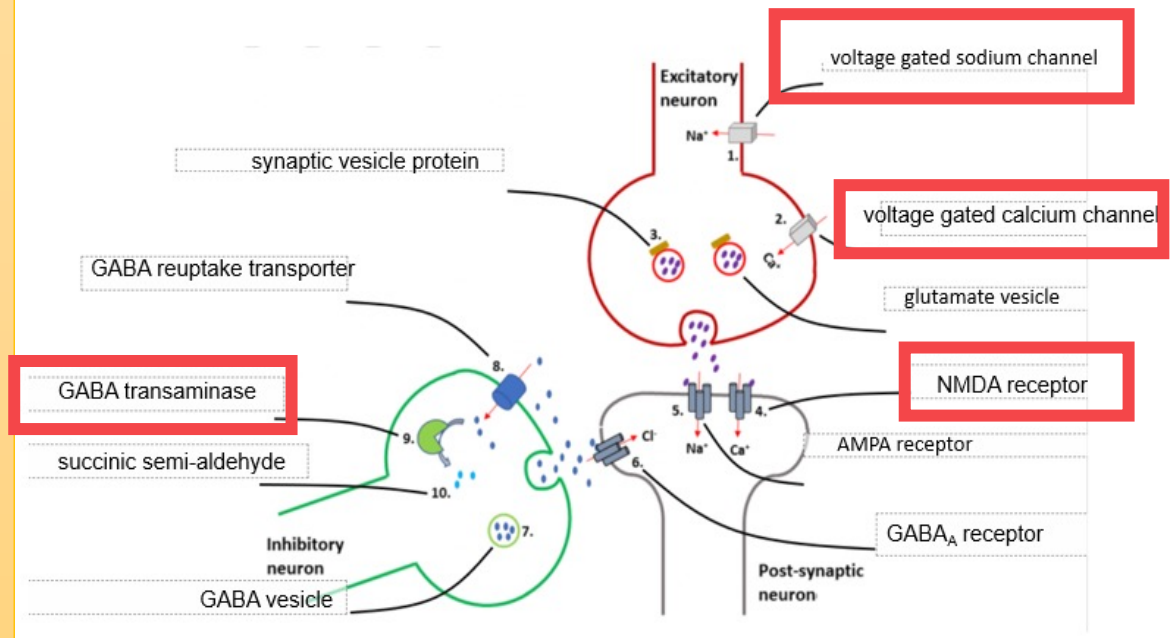
*This drug interferes with vesicle fusion and therefore reduces exocytosis of glutamate thus decreasing the excitatory activation of the post-synaptic neurone.*

# Part 4: Chosen approach to treatment

Q. The neurologist chose not to prescribe sodium valproate to Miss F since it is an anti-epileptic drug that should not be used in female patients with childbearing potential. Sodium valproate has low selectivity. What does this mean and what are the potential consequences of this?

*Valproate is a non-selective drug – it acts on multiple targets i.e. voltage gated sodium channels, GABA transaminase, voltage gated calcium channels, NMDA receptor blockade and even enhances the production of GABA. The biggest problem with non-selective drugs is the propensity for a larger number of side effects due to hitting so many targets.*

***NB is also teratogenic – hence its avoidance in females of childbearing age. The mechanism of this is unknown but may involve inhibition of folate receptors***




**Nervous system disorders:** Describe the clinical features and treatment options of central and peripheral nervous system disorders.