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- Epilepsy is a neurological disorder that is characterized by an enduring predisposition to generate epileptic seizures and the associated cognitive, psychological and social consequences
  - An epileptic seizure is a transient behavioural change that might be objective signs or subjective symptoms (such as loss of awareness, stiffening, jerking, a sensation that rises from the abdomen to the chest, a smell of burnt rubber or déjà vu), caused by abnormal excessive or synchronous neuronal activity in the brain
    - Seizure onset can be
      - Focal (when abnormal neuronal activity arises in one or more localized brain regions or hemisphere),
      - Generalized (when abnormal neuronal activity begins in a widespread distribution over both hemispheres)
      - Unknown (if the available clinical and laboratory data cannot identify whether the onset is focal or generalized)

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- Epilepsy has no identifiable cause, although it may develop after brain damage, such as trauma, stroke, infection or tumour growth, or other kinds of neurological disease, including various inherited neurological syndromes
  - The particular symptoms produced depend on the function of the region of the brain that is affected. Thus, involvement of the motor cortex causes convulsions, involvement of the hypothalamus causes peripheral autonomic discharge, and involvement of the reticular formation in the upper brain stem leads to loss of consciousness

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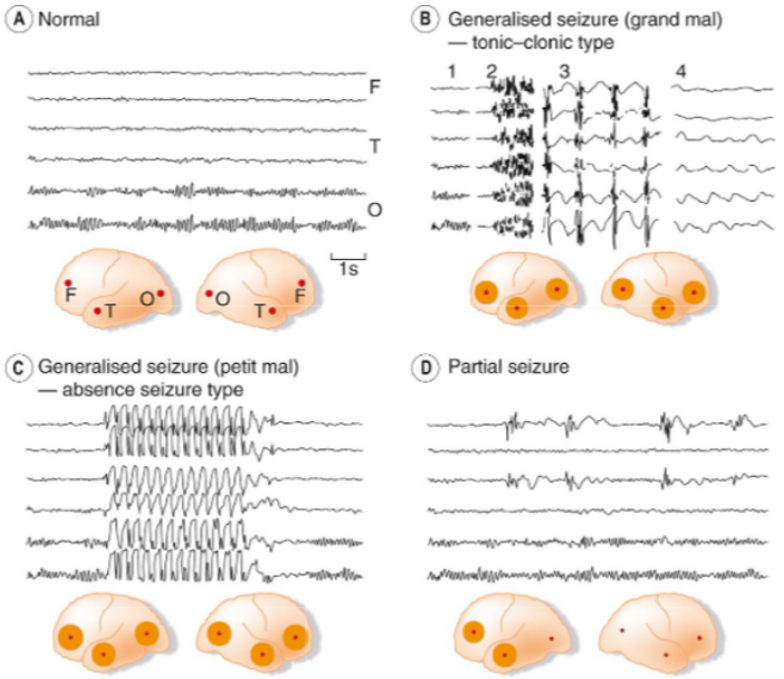
- The clinical classification of epilepsy is done on the basis of the characteristics of the seizure rather than on the cause or underlying pathology. There are two major seizure categories, namely
  - Partial (localised to part of the brain)
    - Jacksonian epilepsy
    - Psychomotor epilepsy
  - Generalised
    - Tonic–clonic
    - Myoclonic
    - Tonic
    - Atonic
    - Clonic
    - Absence seizures



Frontal (F), Temporal (T) and occipital (O) brain sites

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- The neurochemical basis of the abnormal discharge is not well understood. It may be associated with enhanced excitatory amino acid transmission, impaired inhibitory transmission or abnormal electrical properties of the affected cells
- Repeated epileptic discharge can cause neuronal death (excitotoxicity)
- Most genes associated with familial epilepsies encode neuronal ion channels closely involved in controlling action potential generation, such as voltage-gated sodium and potassium channels, GABA receptors and nicotinic acetylcholine receptors
- Some other genes encode proteins that interact with ion channels
- Current drug therapy is effective in 70–80% of patients

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Epilepsy is treated mainly with drugs, although brain surgery may be used for suitable severe cases

Current antiepileptic drugs are effective in controlling seizures in about 70% of cases, but their use is often limited by side effects

In addition to their use in patients with epilepsy, antiepileptic drugs are used to treat or prevent convulsions caused by other brain disorders

- Trauma
- Infection
- Brain tumours
- Stroke

Some antiepileptic drugs have been found to have beneficial effects in non-convulsive disorders such as

- Neuropathic pain
- Bipolar depression
- Anxiety

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- Antiepileptic or anticonvulsant drugs
  - Mechanism of Action
    - Antiepileptic drugs aim to inhibit the abnormal neuronal discharge rather than to correct the underlying cause. Three main mechanisms of action appear to be important:
      - Enhancement of GABA action
      - Inhibition of sodium channel function
      - Inhibition of calcium channel function
    - More recently newer drugs with other, novel mechanisms of action have been developed

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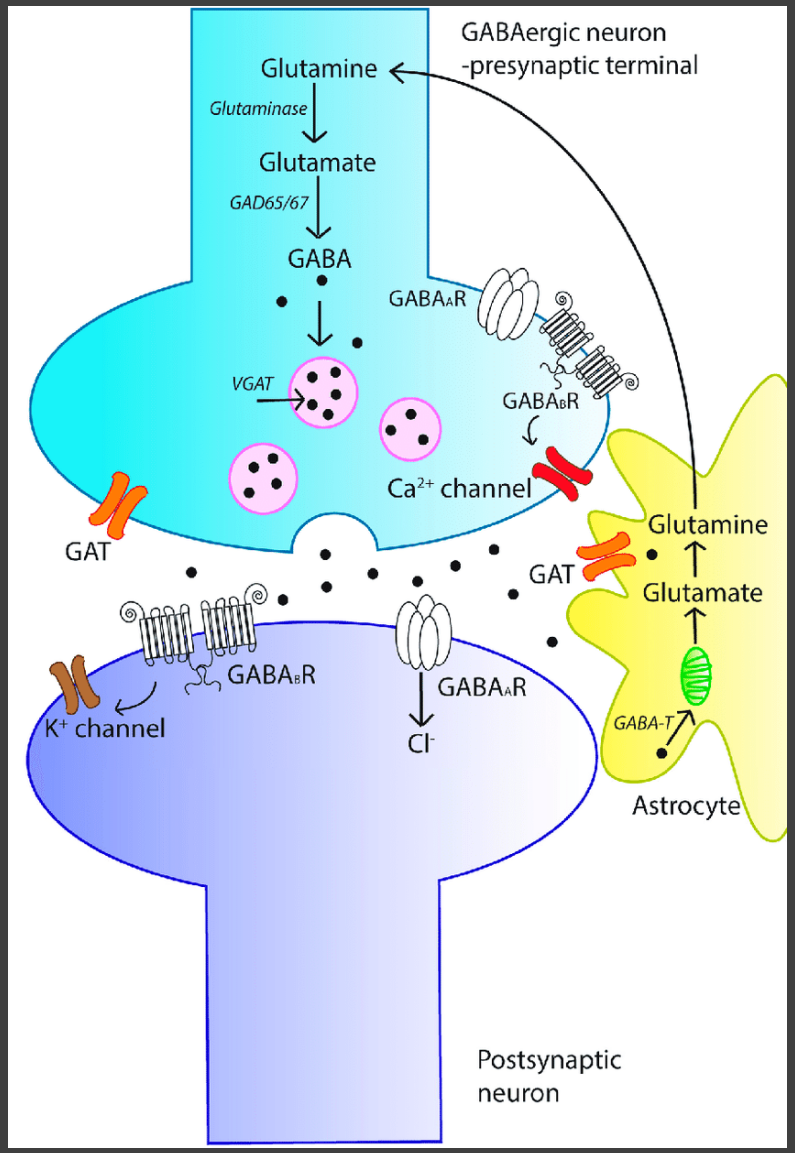
- GABAergic transmission
  - γ-aminobutyric acid (GABA) is the major neurotransmitter with inhibitory function in the central nervous system of mammals
  - GABA is produced by decarboxylation of glutamic acid by the glutamate decarboxylase (GAD)
  - GABA, synthesized in the cytoplasm, is stored in synaptic vesicles present in the axon terminals
  - GABA is degraded by GABA-a-ketoglutarate transaminase enzyme (GABA-T), which deaminates it to succinate semialdehyde; this is oxidized by NAD-dependent succinate semialdehyde dehydrogenase to form succinic acid and enters the Kreb cycle



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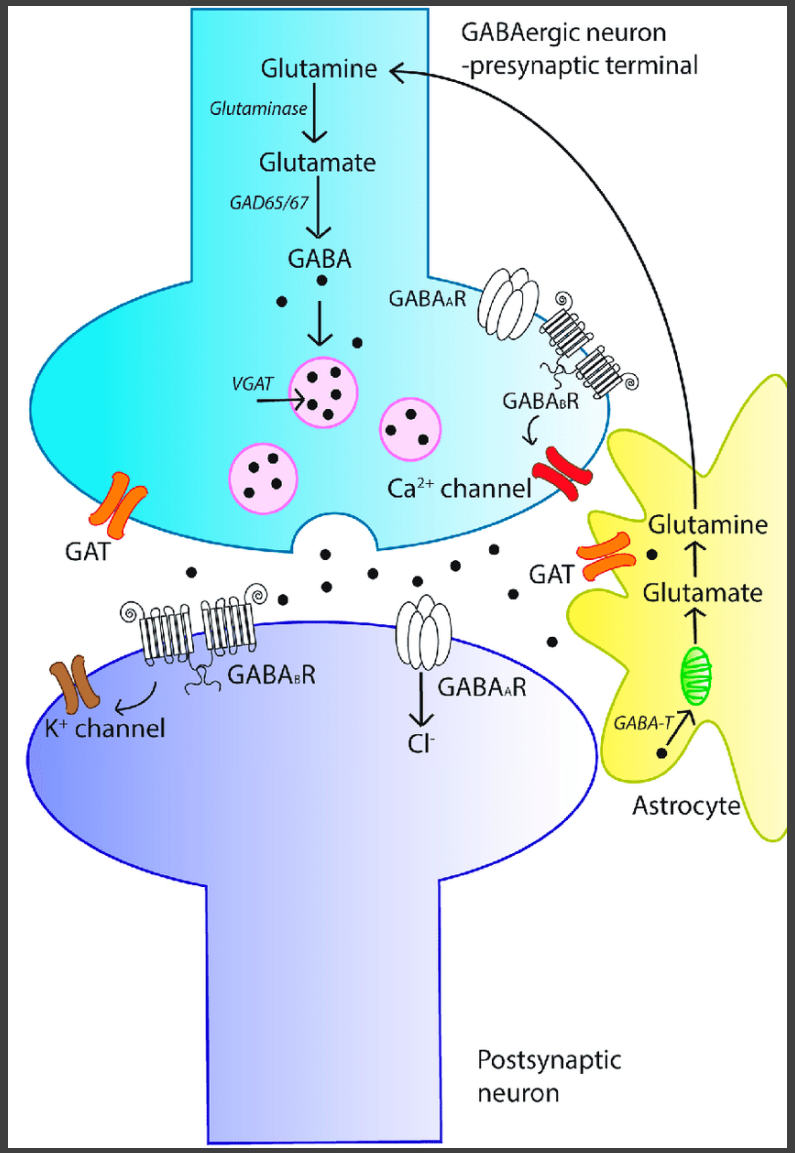
- GABAergic transmission
  - GABA is released either spontaneously or upon nerve stimulation
    - GABA release induced by depolarization is Ca^{++} dependent phenomenon
  - Multiple carriers proteins (GAT) are present in GABAergic endings, which rapidly remove GABA from the synaptic cleft, thus terminating its action. It is believed that preservation of low GABA concentrations in the extracellular space is mainly due to glial transporter activity



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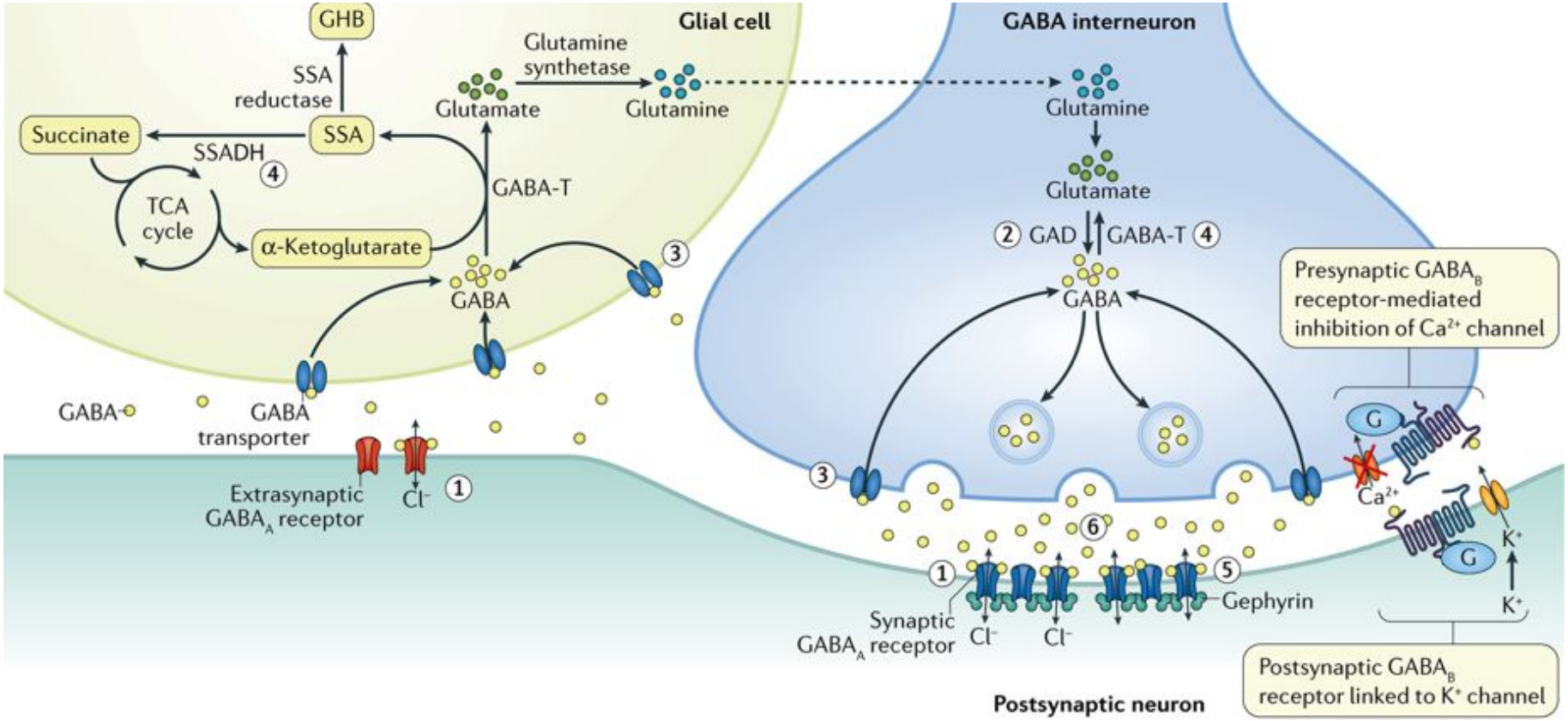
- GABA receptors
  - $GABA_A$ receptors are ligand-gated channels permeable to Cl^- ions
    - GABA a receptors is made of multiple subunits. The $GABA_A$ receptors is a heteromeric complex consisting of five glycoprotein subunits belonging to different classes
    - The most common form of these receptors is represented by a pentamer composed of 2 α-subunits, 2 β-subunits and 1 γ-subunit
  - $GABA_B$ receptors are coupled to inhibitory G proteins


GHB
Glial cell
GABA interneuron
SSA reductase
Glutamine synthetase
Glutamate
Glutamine
Succinate
SSA
SSADH
4
TCA cycle
α-Ketoglutarate
GABA-T
GABA
3
Glutamine
Glutamate
2 GAD
GABA-T 4
GABA
Presynaptic GABA$_B$ receptor-mediated inhibition of Ca^{2+} channel
GABA
GABA transporter
Extrasynaptic GABA$_A$ receptor
Cl$^-$
1
3
G
Ca^{2+}
6
1
5
Gephyrin
K$^+$
G
K$^+$
Synaptic GABA$_A$ receptor
Cl$^-$
Cl$^-$
Postsynaptic GABA$_B$ receptor linked to K$^+$ channel
Postsynaptic neuron

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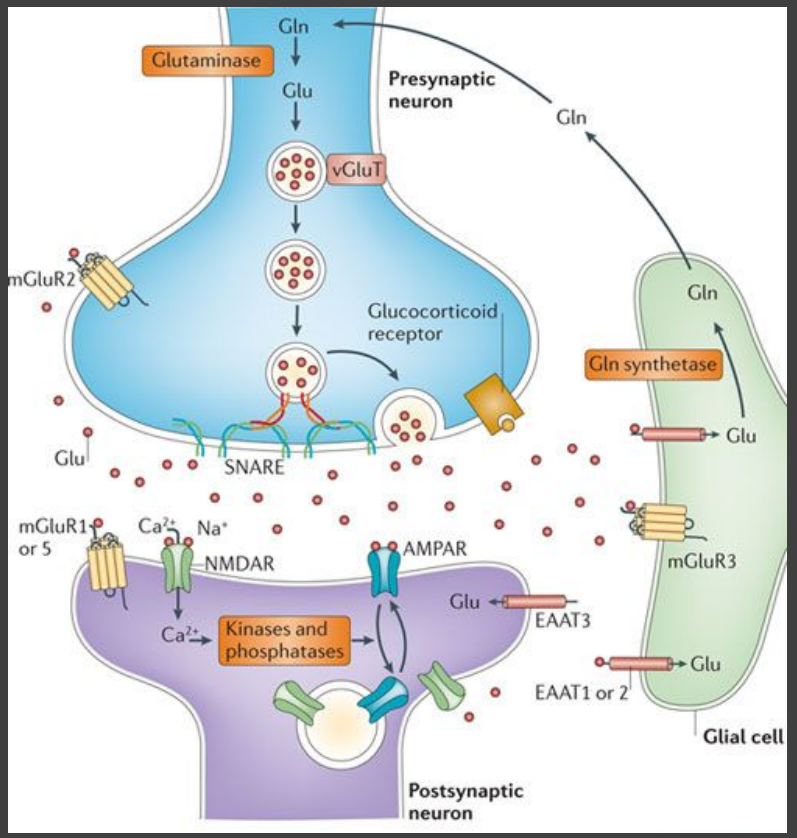
- Glutamate transmission
  - Neuronal glutamate (Glu) is synthesized de novo from glucose (not shown) and from glutamine (Gln) supplied by glial cells. Glutamate is then packaged into synaptic vesicles by vesicular glutamate transporters (vGluTs). SNARE complex proteins mediate the interaction and fusion of vesicles with the presynaptic membrane. After release into the extracellular space, glutamate binds to ionotropic glutamate receptors (NMDA receptors (NMDARs) and AMPA receptors (AMPARs)) and metabotropic glutamate receptors (mGluR1 to mGluR8) on the membranes of both postsynaptic and presynaptic neurons and glial cells. Upon binding, the receptors initiate various responses, including membrane depolarization, activation of intracellular messenger cascades, modulation of local protein synthesis and, eventually, gene expression (not shown). Surface expression and function of NMDARs and AMPARs is dynamically regulated by protein synthesis and degradation and receptor trafficking between the postsynaptic membrane and endosomes. The insertion and removal of postsynaptic receptors provide a mechanism for long-term modulation of synaptic strength. Glutamate is cleared from the synapse through excitatory amino acid transporters (EAATs) on neighbouring glial cells (EAAT1 and EAAT2) and, to a lesser extent, on neurons (EAAT3 and EAAT4). Within the glial cell, glutamate is converted to glutamine by glutamine synthetase and the glutamine is subsequently released by System N transporters and taken up by neurons through System A sodium-coupled amino acid transporters to complete the glutamate–glutamine cycle



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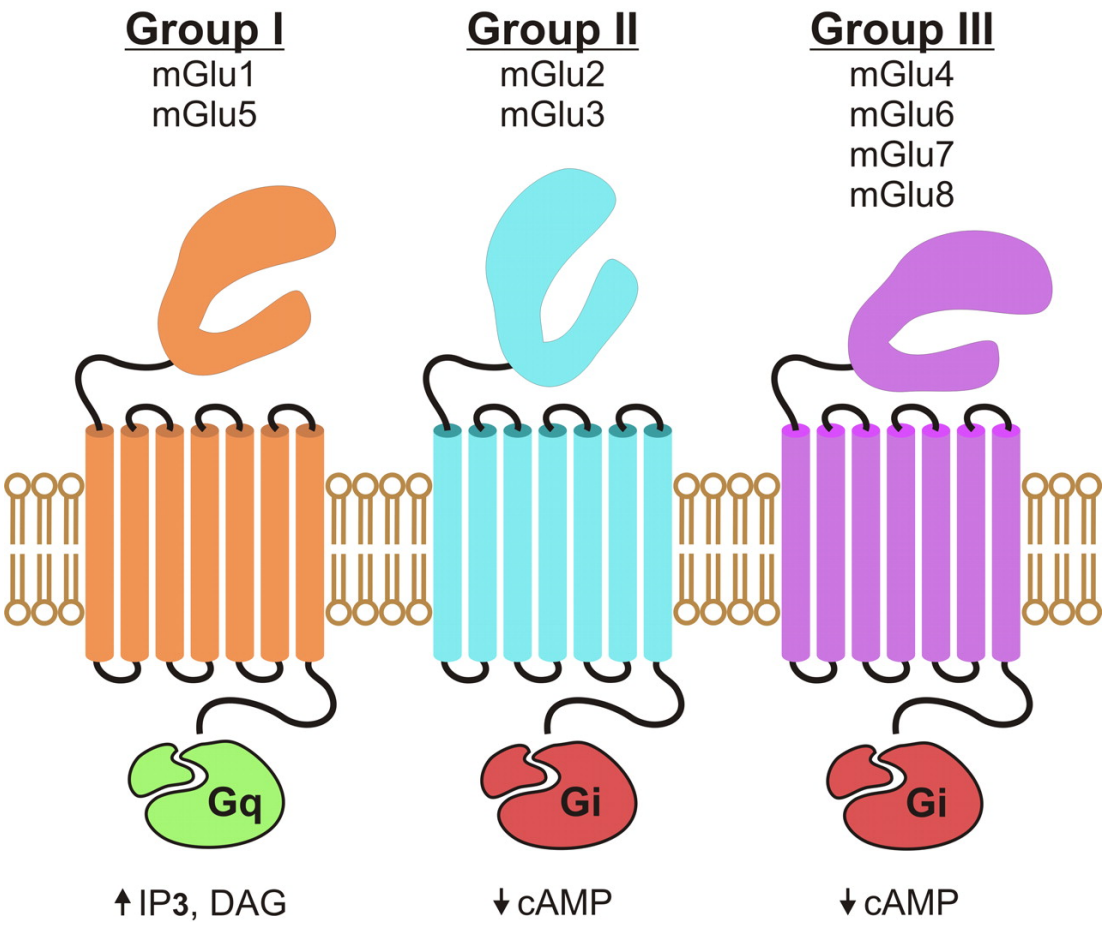
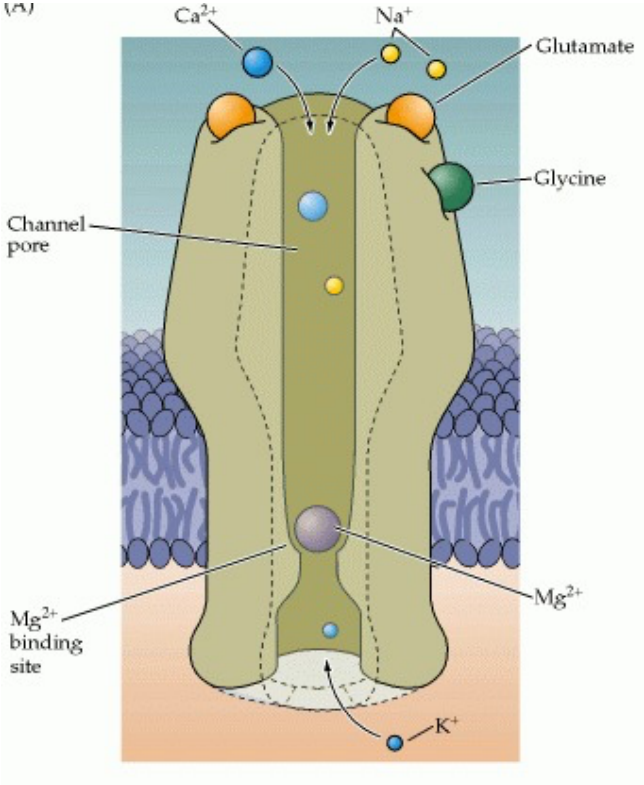
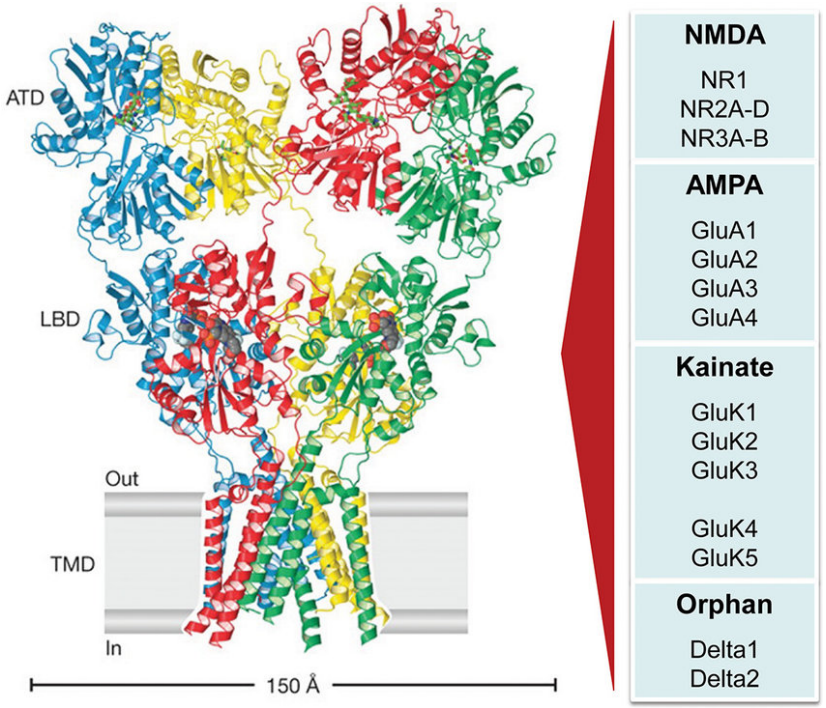

Group I
mGlu1
mGlu5
Group II
mGlu2
mGlu3
Group III
mGlu4
mGlu6
mGlu7
mGlu8
Gq
Gi
Gi
↑IP3, DAG
↓cAMP
↓cAMP





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- Glutamate receptors
  - NMDA receptors
  - AMPA receptors
  - Kainate receptors

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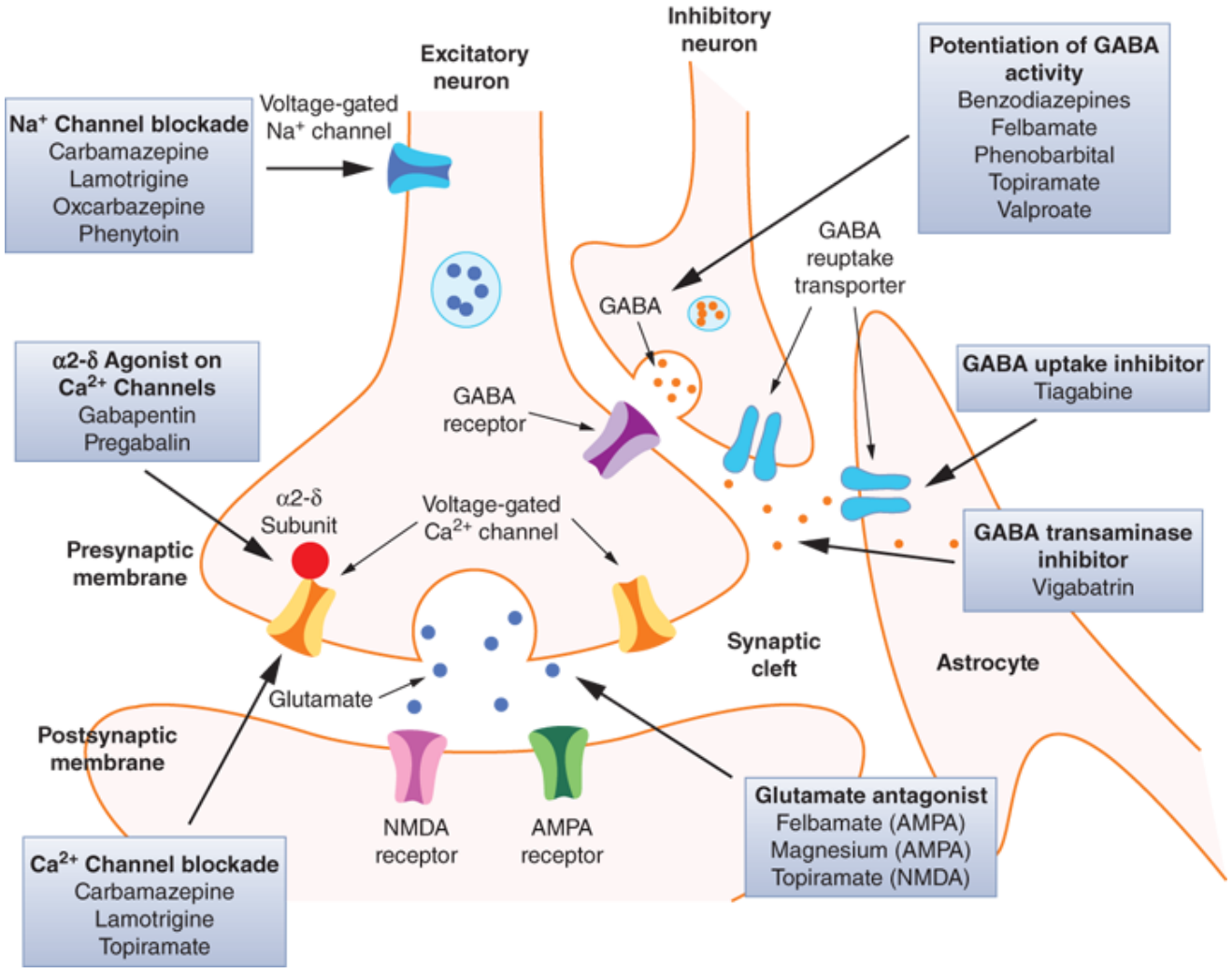
Inhibitory neuron
Excitatory neuron
Potentiation of GABA activity
Benzodiazepines
Felbamate
Phenobarbital
Topiramate
Valproate
Na+ Channel blockade
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Voltage-gated Na+ channel
GABA reuptake transporter
GABA
α2-δ Agonist on Ca2+ Channels
Gabapentin
Pregabalin
GABA receptor
GABA uptake inhibitor
Tiagabine
α2-δ Subunit
Voltage-gated Ca2+ channel
Presynaptic membrane
GABA transaminase inhibitor
Vigabatrin
Synaptic cleft
Astrocyte
Glutamate
Postsynaptic membrane
NMDA receptor
AMPA receptor
Glutamate antagonist
Felbamate (AMPA)
Magnesium (AMPA)
Topiramate (NMDA)
Ca2+ Channel blockade
Carbamazepine
Lamotrigine
Topiramate

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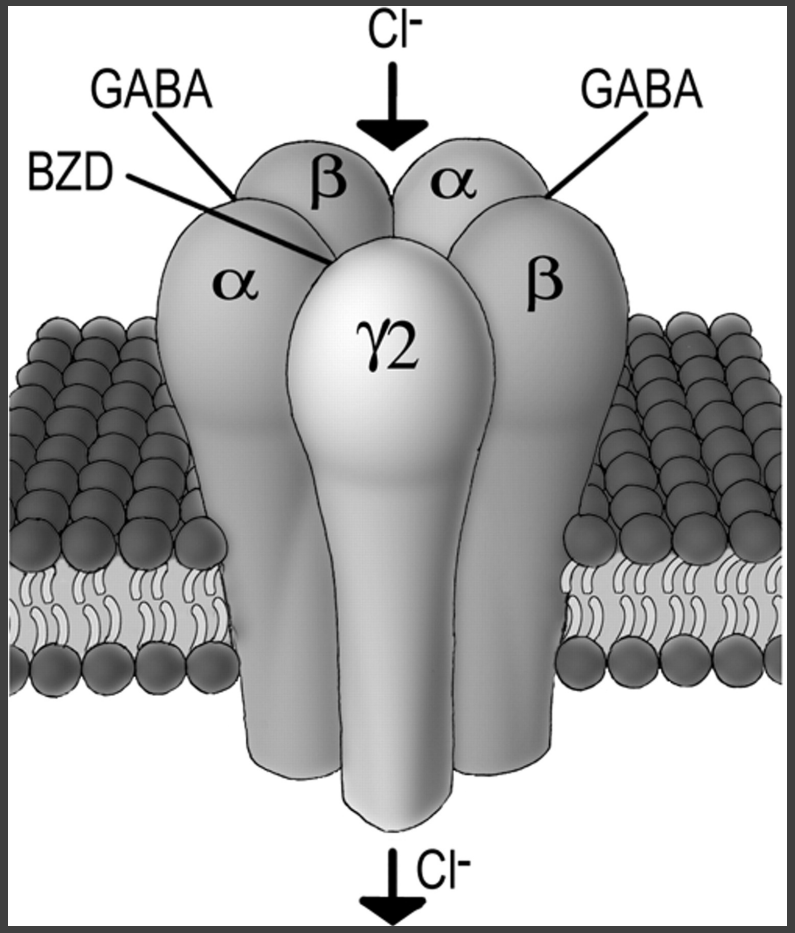
- Benzodiazepines
  - Central benzodiazepine receptor
    - Interaction with benzodiazepines increase GABA ability to activate the Cl- channel
    - Benzodiazepines act allosterically to increase the affinity of GABA for the receptor. Single-channel recordings show an increase in the frequency of channel opening by a given concentration of GABA, but no change in the conductance or mean open time, consistent with an effect on GABA binding rather than the channel-gating mechanism
    - This effect results in reduction of anxiety, sedation, hypnosis and muscle relaxation
      - Diazepam
      - Lorazepam
      - Clonazepam



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- Benzodiazepines
  - Pharmacokinetic Aspects
    - Benzodiazepines are well absorbed when given orally, usually giving a peak plasma concentration in about 1h
    - They bind strongly to plasma protein, and their high lipid solubility causes many of them to accumulate gradually in body fat
    - They are normally given by mouth but can be given intravenously (e.g. diazepam in status epilepticus, midazolam in anaesthesia) or rectally
    - Intramuscular injection often results in slow absorption
    - They are all metabolised and eventually excreted as glucuronide conjugates in the urine. They vary greatly in duration of action and can be roughly divided into short-, medium- and long-acting compounds. Duration of action influences their use
      - Short-acting compounds being useful hypnotics with reduced hangover effect on wakening
      - Long-acting compounds being more useful for use as anxiolytic and anticonvulsant drugs
    - Several are converted to active metabolites such as N-desmethyldiazepam (nordiazepam), which has a half-life of about 60 h, and which accounts for the tendency of many benzodiazepines to produce cumulative effects and long hangovers when they are given repeatedly

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- Benzodiazepines
  - Unwanted Effects
    - These may be divided into
      - Toxic effects resulting from acute overdosage
        - Benzodiazepines in acute overdose are considerably less dangerous than other anxiolytic/hypnotic drugs (barbiturates)
        - In overdose, benzodiazepines cause prolonged sleep, without serious depression of respiration or cardiovascular function
        - The availability of an effective antagonist, flumazenil, means that the effects of an acute overdose can be counteracted
      - Unwanted effects occurring during normal therapeutic use
        - Drowsiness, confusion, amnesia and impaired coordination, which considerably impairs manual skills such as driving performance
      - Tolerance and dependence
        - Tolerance (i.e. a gradual escalation of dose needed to produce the required effect) occurs with all benzodiazepines
        - There may be selective loss of membrane $GABA_A$ receptors containing the α2 subunit
        - At the receptor level, the degree of tolerance will be governed both by the number of receptors occupied (i.e. the dose) and the duration of receptor occupancy (which may vary according to the therapeutic use). Therefore, marked tolerance develops when benzodiazepines are used continuously to treat epilepsy
        - Benzodiazepines produce dependence, and this is a major problem

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- Barbiturates
  - The allosteric binding sites for barbiturates and their antagonist lie within or close to the Cl^- channel. This localization is of fundamental importance
    - Unlike benzodiazepines, barbiturates can enhance Cl^- conductance even in the absence of GABA (GABA-mimetic effect)
      - Phenobarbital

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- Barbiturates
  - Phenobarbital
    - Most barbiturates have anticonvulsant activity, but only phenobarbital which is converted to the active metabolites pentobarbital can exert maximum anticonvulsant activity at a lower dosage compared to hypnotic substances
    - Enhancement of GABA inhibitory effects and direct action on the receptor Cl^- channel function are two of the most important mechanisms responsible for the antiepileptic properties of barbiturates
    - Phenobarbital is effective in the control of generalized tonic–clonic seizures as well as simple and complex partial seizures
    - Their clinical use is limited because of its sedative effects
    - An interesting fact is that their antiepileptic activity seldom fades over time

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- Benzodiazepines – Barbiturates
  - Barbiturate administration results in a functional activation of all central GABAergic synapses with generalized, dose-dependent depression of the CNS with blockade of respiratory center and death
  - It is worth to remembering that benzodiazepines modulate receptor channel function by facilitating GABA action and are completely ineffective in the absence of GABA
  - The CNS depressant effects of benzodiazepines are self-limiting and variable in extent between brain areas and generally they do not lead to death by respiratory depression

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- Leveritacetam
  - Levetiracetam appears to prevent seizure activity via the selective inhibition of hypersynchronized epileptiform burst firing without affecting normal neuronal transmission, though the exact mechanism through which this occurs is unclear
  - The exact mechanism through which levetiracetam exerts its anti-epileptic effects is unclear, but is thought to be unique amongst other anti-epileptic medications. Current knowledge suggests that levetiracetam's binding to synaptic vesicle protein 2A (SV2A) is a key driver of its action
  - SV2A is a membrane-bound protein that is found on synaptic vesicles. It appears to play a role in vesicle exocytosis and in the modulation of synaptic transmission by increasing the available amount of secretory vesicles available for neurotransmission
  - Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release, but this action does not appear to affect normal neurotransmission

- Felbamate
  - Felbamate is an antiepileptic indicated as monotherapy or as an adjunct to other anticonvulsants for the treatment of partial seizures resulting from epilepsy
  - The mechanism by which felbamate exerts its anticonvulsant activity is unknown, but felbamate may be an antagonist of the N-methyl-D-aspartate (NMDA) receptor-ionophore complex. Antagonism of the NMDA receptor glycine binding site may block the effects of the excitatory amino acids and suppress seizure activity

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- VIGABATRIN
  - It is a GABA analog effective in infantile spasms (West syndrome) and as adjunctive therapy in partial epilepsy refractory to other treatments
  - Vigabatrin inhibits GABA-T, resulting in an increase in GABA synaptic concentration and consequent enhancement of GABAergic transmission
  - Unwanted effect
    - Visual field loss

- TIAGABINE
  - Effective in partial epilepsy refractory to other treatments
  - It exerts its anticonvulsant effect by inhibiting GABA re-uptake at the synaptic level through selective blockade of GAT1 transporter

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- Sodium channel blockers
  - Many antiepileptic drugs affect membrane excitability by an action on voltage-dependent sodium channels which carry the inward membrane current necessary for the generation of an action potential
  - These drugs block preferentially the excitation of cells that are firing repetitively, and the higher the frequency of firing, the greater the block produced
  - These drugs bind preferentially to Na^{++} channels in the inactivated state, preventing them from returning to the resting state, and thus reducing the number of functional channels available to generate action potentials
    - Carbamazepine
    - Phenytoin

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- Sodium channel blockers
  - Carbamazepine
    - Pharmacokinetic aspects
      - Carbamazepine is slowly but well absorbed after oral administration. Its plasma half-life is about 30 h when it is given as a single dose, but it is a strong inducer of hepatic enzymes, and the plasma half-life shortens to about 15 h when it is given repeatedly
      - Unwanted effects
        - Carbamazepine produces a variety of unwanted effects ranging from drowsiness, dizziness and ataxia to more severe mental and motor disturbances It can also cause water retention and a variety of gastrointestinal and cardiovascular side effects. The incidence and severity of these effects is relatively low, however, compared with other drugs. Severe bone marrow depression, causing neutropenia, and other severe forms of hypersensitivity reaction can occur, especially in people of Asian origin

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- Sodium channel blockers
  - Phenytoin
    - Despite its many side effects and unpredictable pharmacokinetic behaviour, phenytoin is widely used, being effective against various forms of partial and generalised seizures, although not against absence seizures, which it may even worsen
    - Pharmacokinetic aspects
      - Phenytoin has certain pharmacokinetic peculiarities that need to be taken into account when it is used clinically. It is well absorbed when given orally, and about 80–90% of the plasma content is bound to albumin
      - Phenytoin is metabolised by the hepatic mixed function oxidase system and excreted mainly as glucuronide
      - The metabolism of phenytoin itself can be either enhanced or competitively inhibited by various other drugs that share the same hepatic enzymes
      - The metabolism of phenytoin shows the characteristic of saturation. The consequences of this are that
        - The plasma half-life (approximately 20h) increases as the dose is increased
        - The steady-state mean plasma concentration, achieved when a patient is given a constant daily dose, varies disproportionately with the dose
      - Unwanted effects
        - The milder side effects include vertigo, ataxia, headache and nystagmus, but not sedation. At higher plasma concentrations, marked confusion with intellectual deterioration occurs. Hyperplasia of the gums often develops gradually, as does hirsutism. Megaloblastic anaemia, associated with a disorder of folate metabolism, sometimes occurs, and can be corrected by giving folic acid

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- Calcium channel blockers
  - Drugs that are used to treat absence seizures (e.g. all appear to share the ability to block P/Q-type high-voltage-activated calcium channels or T-type low-voltage-activated calcium channels). T-type channel activity is important in determining the rhythmic discharge of thalamic neurons associated with absence seizures
    - Ethosuximide (low-voltage-calcium channels)
    - Valproate (low-voltage-calcium channels)
    - Gabapentin (high-voltage-calcium channels)
    - Pregabalin (high-voltage-calcium channels)
    - Lamotrigine (high-voltage-calcium channels)
    - Topiromate (high-voltage-calcium channels)
    - Zonisamide (low-voltage-calcium channels)

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- Calcium channel blocker
  - Valproate
    - It is effective in many kinds of epilepsy, being particularly useful in certain types of infantile epilepsy, where its low toxicity and lack of sedative action are important, and in adolescents who exhibit both tonic–clonic or myoclonic seizures as well as absence seizures, because valproate (unlike most antiepileptic drugs) is effective against each
    - Valproate works by several mechanisms
      - Ca^{++} channel blocker
      - Inhibitor of GABA-T and succinic semialdehyde dehydrogenase
      - Na^{++} channel blocker

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- Calcium channel blockers
  - Valproate
    - Pharmacokinetic aspects
      - Valproate is well absorbed orally and excreted, mainly as the glucuronide, in the urine, the plasma half-life being about 15 h
    - Unwanted effects
      - The most serious side effect is hepatotoxicity

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- Calcium channel blockers
  - Ethosuximide
    - The main drug used to treat absence seizures; may exacerbate other forms
    - Acts by blocking T-type calcium channels
    - Relatively few unwanted effects, mainly nausea and anorexia

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- Calcium channel blockers
  - Gabapentin
    - Gabapentin, though designed as a simple analogue of GABA that would be sufficiently lipid soluble to penetrate the blood–brain barrier, owes its antiepileptic effect mainly to an action on P/Q-type calcium channels. By binding to a particular channel subunit (α2δ1)
    - Gabapentin reduces the trafficking to the plasma membrane of calcium channels containing this subunit, thereby reducing calcium entry into the nerve terminals and reducing the release of various neurotransmitters and modulators
    - It is effective against partial seizures. Its side effects (sleepiness, headache, fatigue, dizziness and weight gain) are less severe than with many antiepileptic drugs
    - Pharmacokinetic aspects
      - The absorption of gabapentin from the intestine depends on the L-amino acid carrier system and shows the property of saturability, which means that increasing the dose does not proportionately increase the amount absorbed. This makes gabapentin relatively safe and free of side effects associated with overdosing. Its plasma half-life is about 6 h, requiring dosing two to three times daily
      - This drug are excreted unchanged in the urine they must be used with care in patients whose renal function is impaired

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- Other Uses of Antiepileptic Drugs
  - Antiepileptic drugs have proved to have much wider clinical applications than was originally envisaged, and clinical trials have shown many of them to be effective in the following conditions:
    - Bipolar disorder (valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate)
    - Migraine prophylaxis (valproate, gabapentin, topiramate)
    - Anxiety disorders (gabapentin)
    - Neuropathic pain (gabapentin, pregabalin, carbamazepine, lamotrigine)
  - This surprising multiplicity of clinical indications may reflect the fact that similar neurobiological mechanisms, involving synaptic plasticity and increased excitability of interconnected populations of neurons, underlie each of these disorders

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- Antiepileptic Drugs and Pregnancy
  - There are several important implications for women taking antiepileptic drugs
    - By inducing hepatic CYP3A4 enzymes, some antiepileptic drugs may increase oral contraceptive metabolism, thus reducing their effectiveness
    - Taken during pregnancy, drugs such as phenytoin, carbamazepine, lamotrogine, topiramate and valproate are thought to produce teratogenic effects
    - Induction of CYP enzymes may result in vitamin K deficiency in the newborns