Continuation of fast neurotransmitters:

- The main fast excitatory neurotransmitter is glutamate.
- The main fast inhibitory neurotransmitter is GABA - GABA is mainly present in the brain, its percentage in brain is more than glutamate. This is because every large glutamate neuron is surrounded with more inhibitory substances. It is said that GABA is 5 times more in number than glutamate.
-Most of the small inhibitory inter-neurons are GABA neurons and because they are fast conducting neurons, their receptors will be ionotropic.

- There are two families of GABA and the most known one is GABA- A (with ionotropic receptors). GABA-B is the less known one and works through G protein coupled receptor (metatropic).
-The inhibitory GABA receptors with ionotropic receptors will open Cl ion channels causing inhibition of cells. These receptors have more than one site for allosteric modulators.

Allosteric modulators will be discussed later on in this course when we study the treatment of epilepsy. The most important allosteric modulators include:
1- barbiturate
2- benzodiazepine

Other areas may be blocked by toxins. For example, blocking of GABA will results in a decrease of its inhibition action in that area.

Alcohol is one of the allosteric modulators for GABA ion channels. When it binds to GABA, the ion channels will be open and more Cl ions will enter. Alcohol’s function is dependent on GABA; alcohol won’t work if GABA is absent.

Recall that allosteric modulators bind to a site different from that of the neurotransmitter. However, if both the neurotransmitter and the allosteric modulator bind together then they will result in opening a greater number of receptors or opening them for a longer time.
There is an experiment which illustrates the effect of an allosteric modulator. (slides 50 and 51)

P: represents GABA , and the base line
v: isn’t included
i: the amount , and the time of current of one Cl ion channel
- Because GABA opens Cl channel ,the current will be negative.
-On base line : there is no current because the receptor is closed !
-The channel opens with the presence of GABA, and closes with its absence.

-if we put GABA + diazepam ( an allosteric modulator ), the current will be greater than with GABA alone.
Note that, diazepam alone >>> no change
diazepam +GABA. There is wider/greater opening of channels and hence more current

slide #55

GABA is made by a direct step from glutamate.

GABA transporter is used for the uptake of GABA. Usually this transporter is the astrocyte ( a glial cell).

Number of GABA producing neurons is 5 times more than that of glutamate.
 \*cortex is composed mainly of:
1- GABA
2-glutamate

one of them is excitatory and the other is inhibitory. They are also synthesized from each other forming a cycle. Intermediate to them is a glial cell –ASTROCYTE- .

Since some neurons synthesize GABA and others synthesize glutamate, ASTROCYTE is an intermediate between them creating a balance between the excitatory and inhibitory neurons (allowing proper function).
GABA producing neurons convert glutamine to glutamate then glutamate is used to produce GABA.

Glutamate producing neurons produce glutamate from glutamine.

There is a pool of glutamine and this glutamine is either converted to glutamate or GABA ☺
 **PAY ATTENTION:**  the intermediate in GABA – glutamate cycle is the astrocyte and its function is to recycle GABA and glutamate to glutamine.

If there is an imbalance in the cycle, seizures/epilepsy results.
epilepsy: An imbalance between the excitatory and the inhibitory activity of the brain.

**EEG (electroencephalography):**electro: related to electricity
encephalo : related to the brain
graphy : writing or representation of the brain

procedure:

Sensitive electrodes attached to an amplifier are placed on the skull. These electrodes sense the difference in electricity in the brain >>>> transmit it to the amplifier which enlarges it. The result is a drawing of the electrical activity of the brain.

EEG doesn’t record the activity of a certain channel in the brain, but it records the differences of activity that are detected by the electrodes. So when firing of glutamate or GABA occurs, both up and down waves will be seen. EEG also shows the synapses of neurons (even those which did not reach the threshold). Why? Because it detects currents and movement of ions.

Conclusion: Excitation is NOT represented by ascending waves and inhibition is NOT represented by descending waves. Hence, the activity shown may be represented by glutamate neurons, GABA neurons or even synapses of neurons.

We perform the EEG on the surface of the cortex. The disadvantages are the distance between the electrodes and the actual cortex. Also, the presence of isolators. So the EEG actually records an area on the cortex not one or two neurons. It is said that up to 200 neurons should be activated until the activity can be recorded (less are non-recordable).

Recall that glutamate usually exists in pyramidal cells ( big neuron) and GABA usually exists in inter neurons ( small neuron).
 Logically we would think that we should record larger neurons because the activity will be shown when about 100-200 neurons are active. On the other hand for the small neurons to be recorded 300-400 GABA cells need to be active. In fact, both will be recorded by the EEG.

 **slide #57**
to record an EEG we put electrodes on surface of the brain, only a small signal will be taken and transported to an amplifier which will in turn enlarge it. The signal is then drawn on paper or on a computer.
**slide #58**
-this is a figure of an EEG
-Electrodes are placed on certain areas of the brain covering all the cortex and surface, each will have a different activity .
-notice that a greater number of electrodes are placed on the occipital area, this is because it has a **higher activity**. The higher activity is due to the presence of **"area of vision**" (since the patient has his eyes opened).

EEG is used in a clinic for two purposes:

1. Identify the presence or absence of the activity in a certain area.
2. Notice an increase or a decrease in the activity with change in time.

Recall the definition of a seizure: “the imbalance between inhibition and excitation presenting extra activity”

"شحنات زايدة بالمخ"

This will be shown on the EEG as "extra activity" so any extra activity of brain is called seizure.

Seizures may or may not show as a motor function.
A patient with recurrent seizures is called an "epileptic patient".

It is not necessary for an epileptic patient to experience tonic or clonic movements. (Which is muscle spasm followed by fainting), this is only one type of epilepsy.

We said that there is an imbalance between excitation and inhibition. For example, if in area (35) the excitation increased, it would lead to the over activity and firing of all of the neurons in that area. Action potentials are continuously conducted since there is no inhibition. Since the axons of these neurons reach other areas, even if the inhibition is normal (no imbalance) there, they will still be excited and fire an action potential. In this way, all areas will be excited. When this excitation reaches the motor cortex, motor neurons will be excited and will descend down as corticospinal tracts and hence all muscles of the body will tense causing tonic and clonic phases. After a while the synapses end, and no action potential is reached, here the brain is completely relaxed and the patient will faint for a while. This is the “Grand mal” epilepsy which involves the whole body and is a general type of epilepsy.

Note: Epilepsy is always excitatory.

Other types of epilepsy include:
 1- Clonic seizure: which has only the clonic phase of epilepsy without tonic phase
 2-Absence seizure: There will be an increase in the brain’s activity without the excitation of motor neurons leading to loss of conscious (without muscle contraction).
 3- Focal type: which is specific to a certain area (not generalized), with or without symptoms, and the patient may know or not know about it.
e.g: 1- seizures in visual cortex: patient will imagine seeing things that are not real.
2- Seizures in auditory cortex: patient will imagine hearing sounds
(different from hallucinations).

Many patients with grand mal epilepsy say that they imagine things or smell scents or hear sounds just before the seizure takes place, this is due to the fact that generalized seizures starts in certain areas and are then distributed throughout the brain, so it may start in the visual area or auditory area and then spread.
This is called "Aura".

Summary :

2/ not all epileptic attacks are followed by fainting
3/ not all fainting occur after a tonic/ clonic phase
3/ some epileptic attacks involve tonic/ clonic phases others don’t
4/ some epileptic attacks have a motor output & some don’t
5/ some epileptic attacks involve absence seizures
6/ some epileptic attacks are generalized, others are focal
7/ some epileptic attacks are accompanied with symptoms, others are not
8/ some epileptic attacks are preceded by aura, others are not

Causes of epilepsy:
1/ primary : (we do not know the cause)
 1- genetic: \* mutation in GABA receptors so they don’t function well
 \* problem in Na/k transporters
 \* problem in enzymes that degrade glutamate or that synthesize it GABA
 2- developmental : anything that affects the brain during the developmental process like trauma.

2/ secondary : (we know the cause)
brain trauma
brain cancer
drugs
infections
all will decrease inhibition in the affected brain areas leading to epilepsy

\* Our brain mainly depends on K & Ca balance, so electrolyte imbalance in the body may cause seizures.
e.g : 1/ hypokalemia means increase in Na compared to K , causing epilepsy.
 2/ food poisoning by certain bacterial toxins which may block GABA ion channels leading to seizures

\*epilepsy = recurrent seizures
 \* it's said that a normal individual experiences an average of 10-20 small seizures throughout his/her life ( those are not felt, and have no effect ).

treatment :
1) mainly by drugs : - by increasing inhibition( so increasing GABA ) & decreasing excitation
e.g: benzodiazepine, barbiturate
 - other new drugs that are targeted to NA/ K transporters, or to decrease the activity of the voltage gated Na ion channels ( to decrease the action potential ). This prevents future attacks.

2) Surgical: by removing the excited area or by cutting pathways in the white matter to keep the epileptic attack focused and prevent its spreading.

\*EEG is usually recorded for 30-60 min, which is a short duration, recently " in hospital EEG" is introduced which records brain activity for 48-72 hours
\* EEG is never done shortly after the attack because there will be no brain activity.
\* EEG is never 100% diagnostic except at the time of attack, meaning that normal EEG doesn't exclude the possibility of epilepsy.
\* epileptic patients may experience different types of epilepsy throughout his life
e.g : An absence seizure patient may experience 1-2 generalized attacks in one year.
 A focal seizure patient -during stressful periods- may experience generalized seizures.

\*Types of epilepsy may change with changing environment, stresses and mechanisms of life.
\* Usually if epilepsy started at a young age it will regress with time.

