

## The Cerebral Cortex and Higher Intellectual Functions

The Cerebral cortex consists of 2 cerebral hemisphere and each hemisphere consists of 5 lobes (frontal , parietal ,temporal ,occipital ,insular lobe which is the hidden lobe between the temporal lobe and parietal or frontal lobe) each one of these lobes has a function and each one them has different gyri with different function. The lobes are also subdivided based on the site or architecture of the neurons.

**The neocortex** (which is the cortex present in "new" animals or highly developed animals ) represents the great majority of the cerebral cortex. It has 6 layers numbered from superficial to deep. The structure of the neocortex is relatively uniform, however, there are exceptions since we have a certain area in brain where the cortex has only 3 layers and we have areas consisting of 4 layers only. Now when we say neocortex we mean the 6 layer cortex. Each cortical layer contains different neuronal shapes, sizes and density as well as different organizations of nerve fibers.

They are 6 layers with different (site or architecture /distribution of neurons /thickness of each layers ). This is according to **Brodmann's classification**. He divided the cortex in to 50 areas and these areas differ in their architecture and shape. Brodmann found that "forms follow function" = when we have differences in the site, architecture or distribution of the neurons they will have different functions. So we have different types of neurons and their shape is determined by the shape of the cell body and the distribution of the dendrites, each neuron is specialized in certain way, has a different process, and present in a certain layer in a certain amount. The most famous and most abundant neurons are the pyramidal neurons (the name refers to their shape: the shape of the cell body is pyramidal).

**Each layer in the 6-layered neocortex** has certain functions and forms certain connections:

**1- Layer one** almost has no cell bodies, and even the cell bodies present form very local connections.

**2- Layer two and layer three** make a long connection "cortical to cortical connection" and usually this connection is within the same hemisphere and the same lobe. Although, there are some parts in these 2 layers that connect to the contralateral hemisphere and to other lobes. These 2 layers are responsible for processing when we want to integrate more than one function: the supplementary motor area usually communicates with the 2 cerebral cortices and this is done by the help of 2+3 layers.

**3-Layer four** usually the input of every sensation that come through the thalamus, then reach the cortex all will enter layer 4, that's why in the primary somatosensory cortices usually layer 4 is big and prominent because it's the input layer.

**4- Layer five** usually neurons in this layer go down to subcortical structures and to the spinal cord, this layer has the function of going down and giving orders to spinal cord (cortico-spinal), the brain stem and the cerebellum. Due to this function, layer 5 is big in the motor areas.

**5-Layer six** neurons can go down to subcortical structures, mainly to the thalamus and some go to the basal ganglia.

This is why different cortices have different functions and there are also different distributions of the layers: If layers 2+3 prominent → Processing cortex (late association cortex), If layer 4 is the biggest → Sensory cortex (receives information), if layer 5 is the largest → Motor Cortex (gives orders, descend to control the function of brain stem and the cerebellum)

## Neurons

The main cells of the CNS, they communicate with each other through synapses and the synapses are specialized structures that transfer information between 2 neurons or between neuron and an effector cell.

### Synapses are of 2 types:

1- **Electrical synapse**: which is present mainly in the heart, not present in high amount in the CNS and if they were found they would be present between glial cells not between the neurons.

2- **Chemical synapse**: they are more prominent and more famous, include the release of neurotransmitters (released when the AP in the presynaptic neuron triggers entry of Ca, followed by the fusion of the synaptic vesicles with the presynaptic membrane and then release of NT) and these NT bind with receptors in postsynaptic membrane and lead to the opening of certain ion channels, ion flow to the postsynaptic neuron causes changes in its potential, eventually enough to fire an AP.

- **The receptors determine the effect of NT! This is since the response of the postsynaptic neuron depends on the type of receptor they have;**

### We have 2 types of receptors:

1- **Ion channel receptors**: Ionotropic receptors which are ligand-gated ion channels, the NT will bind to the receptor and as a result of this binding these channels will open.

2- **Second messenger receptors**: Metatropic or Metabotropic receptors which work through second messengers. The second messenger receptor can perform many functions such as: activating ion channels, transcription of some enzymes, affecting the DNA, and many others. The most famous second messenger is the G-protein coupled receptors which works through cAMP and may be excitatory or inhibitory to cAMP production. We also have the PLC pathway which works through IP3 and DAG (more involved with Ca although it can activate enzymes and kinases).

- **Differences between the 2 types of receptors:**

\*Ion channels receptors: faster but have a shorter duration.

\*Second messenger receptors: slower but can produce a longer lasting effect, and can have amplification of the signal because each step can do more than one effect.

- **Why do we study receptors? Receptors and NT are the way to interfere with and regulate the CNS**

## Drugs

Drugs facilitate or inhibit activity at synapse, and according to this we classified them as:

1- **Agonist**: work like the NT, interact with the receptor to mimic or increase the effects of neurotransmitters

2- **Antagonist**: block the receptors, prevent the agonist or NT from binding to the receptors and block the function of NT

- If we have both agonist and antagonist what will happen? Partial agonist → half the effect

\*Agonist = effect (occupy receptors and activate them), antagonist = no effect (occupy receptors but don't activate them), both (agonist + antagonist) = partial effect, less activation

3- **Allosteric modulators**: bind to different sites other than the agonist sites and can either block (if it blocks the effect we call it a blocker which is more strong than the antagonist) or can enhance the effect of an agonist.

- The NT will bind to receptors, this binding will open ion channels, now the presence of allosteric modulators will enhance the effects of the ion channels by either making them open on a larger scale or the ion channels will stay open for a longer duration.

- **The effect of each drug depends on:**

1- Concentration of the drug

2- Affinity (tendency to bind to receptors)

3- Efficacy (the tendency of the drug to activate the receptor).

- We study receptors and NT since we are concerned with regulating the function of the CNS therefore we will focus on their synthesis : esp. rate-limiting enzyme and/or substrate, their clearance and inactivation as well as their location and pathway

## Neurotransmitters

- More than 50 types, their actual number can reach 108 NT, and there are many ways for classification of these NT depending on their synthesis, size, how they work...etc

### Physiologically classified into:

1- **Fast working NT**: mainly work through ion channels receptors. Glutamate is the most important one

2- **Slow working NT**: usually work through second messenger.

- Fast working NT: **Glutamate** (synthesis not important to memorize):
  - It's the precursor for GABA
  - Glutamate works through 2 big families of receptors:

**1- Ionotropic**: More famous and more widely spread. Fast working NT. Glutamate is the main excitatory NT in the brain, 95% of excitatory synapses in the brain are glutamatergic.

**2- Metabotropic**: the smallest, less famous, less spread. Slow synaptic transmission, can either be excitatory or inhibitory, mainly work through PLC system involving Ca

- Ionotropic receptors are of 3 types:

**1-NMDA**

**2-AMPA**

**3- Kainate**

These 3 receptors are positive ion channels and they permit mainly Na and Ca to enter

- The differences between these 3 receptors:

**1- Kainate** is the only one usually (not always) that is presynaptic.

**2- NMDA** permit more Ca to enter than Na, and is usually slow-opening with delayed closure, (usually when we have glutamate AMPA will be the first one to open followed by the NMDA which will permit more Ca to enter than Na and will stay open for longer period).

- **Kainate Receptor** is a presynaptic receptors, and will be released usually by the same neurons that release glutamate. It's longer active which is one of the positive feedback loops: when there is release of glutamate, it will bind to the presynaptic receptor Kainate which is an **excitatory** ion channel, this leads Na entry and excitation inducing more voltage changes and more Ca entry, eventually inducing more glutamate release.
- **Clearance of Glutamate - usually we remove glutamate from synapses by:**

1- Degradation through enzymes

2- Picking it up through excitatory Glutamate transporter (picking up glutamate using ATP and permit it to enter back into neuroglial cells such as astrocytes or back into neurons.

- **Important Pathophysiology of glutamate "pathophysiology of a stroke":**

- Stroke: ischemia in the brain. Why does the stroke kill brain cells and doesn't kill that much in skin and muscle cells?

In the case of a stroke there will be no ATP and when there is no ATP we will have more glutamate in the synapses. Why? normally there will be picking up of glutamate by transporter and the transporter depends on the presence of ATP. As a result the NMDA and AMPA receptors are open and permit Na to enter and mainly Ca to enter, so there will be high amount of Ca inside the cell and this will induce apoptosis leading to cell death (cytotoxicity) → increase intracellular Ca, induce apoptosis, killing the cells, that's occur even if the effect of ischemia is not that high.

This is important in the treatment of stroke since by giving the patient an injection in the first 20-30 minute it will relieve the effects of the stroke. This injection contains a drug that is a blocker or antagonist to the NMDA and AMPA receptors. it's beneficial in the first 20-30 minute and is very critical but after an hour the effect is very minor and only decreases the number of cells or neurons exposed to death.

- Glutamate is the main excitatory NT in the brain and it has many side-effects, therefore it is targeted by certain drugs. Dysfunction of glutamatergic transmission may also involve schizophrenia-like symptoms, cognitive dysfunction, Depression and memory impairment.

- **GABA:**

1) Main inhibitory NT.

2) Synthesized from glutamate.

3) Works through two families of receptors and these families are inhibitory through opening of Cl channels and allowing Cl to enter, leading to inhibition:

- **Ionotropic GABA-A receptors:** More famous, more spread. Coupled to an integral **Cl-channel**
- **Metabotropic GABA-B receptors:** Less famous, less spread. G- protein coupled receptor

The receptors of GABA are very famously studied, have many allosteric modulators, many effects.

*Ionotropic GABA-A receptors:*

- An integral chloride channel activated by competitive agonists: GABA and muscimol.
- Blocked by convulsant bicuculline (competitive antagonist) and picrotoxin (noncompetitive antagonist). block the receptors and prevent the function, important in the treatment of seizure.
- Allosterically modulated by benzodiazepines and barbiturates which potentiate the effect of GABA. Also important in the treatment of seizures.
- Slide 52: Benzodiazepines potentiate GABA-induced responses, this is demonstrated:
  - Upper line represents what drug is administered and in what time (we give GABA and continue until certain time where the line flattens).
  - Second line is not important.
  - Third line represents the current which is a down current and clearly there is inhibition (GABA, open ion channels, Cl enter, down current, inhibition)
  - The stage when we give Diazepam which is a positive allosteric modulator for GABA: we gave diazepam but no GABA was present, therefore the receptors are closed → no effect. If we give GABA at the same time and amount as diazepam and for the same duration the receptors will open more and more effect is produced (positive allosteric). Now once the GABA is depleted, diazepam loses its function, so diazepam is only an allosteric modulator and not an agonist and after washing it away the cell returns to its initial state. This explains what's meant by positive allosteric modulators such as (diazepam, barbiturate, benzodiazepines, alcohol, steroid).
- GABA is synthesized from glutamate and this leads to something called the glutamate GABA shunt (GABA metabolism). 99.9% of the cells of the 6 layers of the neocortex contain glutamate or GABA. So GABA and glutamate: 1) are both synthesized in the same way 2) GABA is synthesized from glutamate 3) both are picked up by astrocytes, and astrocytes begin to convert GABA to its precursors which is a source of glutamate in order to re-start the synthesis process, that's why any imbalance in this glutamate-GABA pathway (excitation → increase glutamate and decrease GABA / inhibition → decrease glutamate and increase GABA) will lead to disorders and the most famous one which related to imbalance between excitation and inhibition is **seizures**.

- Before start talking about seizure we will talk about the EEG:
- EEG ( Electroencephalography ) we record signals from skull, EEG produces a graphed representation of the electrical activity occurring in a person's brain.
- Recording start from outside ( scalp ) where we put the electrodes, therefore we have different insulators which doesn't give us very accurate idea about what's happening and the changes that and we can't tell whether the changes are due to glutamate or GABA. It only gives us indication that there are changes.
- Any changes that occur in big number of neurons ( postsynaptic EPSP and IPSP ) can be detected and recorded since there will be an electrical current produced, Na has entered the cell and therefore it will also enter other surrounding cells which produces minor currents. These minor currents when summed up (100-200) will be detected at the surface (small currents created by large numbers of neurons are summated and produce the final detectable / recorded current on the surface)
- We can't determine whether the detected current represents excitatory or inhibitory synapses. A common some people make is that they think that if the line goes up then it's excitatory and if the line goes down then it's inhibitory but this is not true.
- We have to know that the line which goes up 1cm differs from the line which goes up 3 cm (the line which goes up 3 cm indicates extra activity).
- In an EEG one neuron doesn't give a detectable current, if we have one neuron (excitatory) and one neuron (inhibitory) and each one of them makes 2 currents finally they will cancel out each other. We need 100-200 neurons that work in the same condition in the same direction and in the same moment to get a detectable ( recorded ) current.
- Synchronous activity on an EEG indicates higher power. And the line that appears on the graph goes up and down more, and we have an increase in the activity → This is how we detect **seizures**.
- **Seizure:** Abnormal/imbalanced electrical discharge in an area in the brain which can be spread or not and can be detected on EEG usually. Initially synchronous and may or may not have a motor component

**They are classified according to their muscular component/output:**

1) With muscular output: such as tonic الشد and clonic الشد العكسي phases

- Big seizures that lead to complete synchronization, spreads to all brain including the cortex, producing motor effects. And there can also be sensory effects when it spreads to sensory areas such as in case of hallucinations. and from the sensory areas it can spread again to motor

2) No muscular output.

- so seizures can be " with muscular activity / without muscular activity / partial / complete ".

The causes of seizure can be:

**1) idiopathic** (we don't know the reasons), we call it **primary** idiopathic seizure which is the more common than the secondary, may result from:

- developmental problems
- old trauma
- congenital or genetic problems

**2) seizure of known causes**, we call it **secondary** symptomatic seizure, these causes:

- imbalance in the electrolytes leading to imbalance in the neuronal activity producing seizure
- fever lead to seizure + epilepsy
- trauma
- tumors (neoplasm)
- infection

- Anything that affects the glutamate – GABA shunt, or the ways neurons send their axons and dendrites and affect their development, or the axon shape and AP duration will lead finally to imbalances and seizures.
- An imbalance doesn't mean that in every second and every hour there will be a seizure, you have to know that it's a circuit and it constantly has input and output, inhibition and excitation, and seizures occur when there's propagation or synchronous activity including 100, 200 neurons. If we have one neuron and it's always active it will die.

- Every human commonly has 2 seizures undetected during a year.

- If a human has 2 seizures and they were detected and the symptoms appear in the patient then we call it epilepsy.

- The treatment of seizures is either to induce GABA or decrease its activity (it's difficult to touch the glutamate system because it's complicated), so treatment usually occurs by:

1) allosteric modulation of GABA

2) GABA antagonists

3) regulate the excitatory by: Na channels blockers / glutamate synthase inhibitors / GABA synthase inducers.

- **Acetylcholine**

- Ach has a lot of ionotropic receptors in the CNS its generally described as a fast working NT while some books consider it as a neuromodulator.

- Composed of acetyl CoA + choline = Ach + CoA .

- Ach degraded by Ach esterase enzyme .

-Ach receptors :

1) **Muscarinic receptors** ( second messenger ).

2) **Nicotinic receptors** ( ion channels ) .

In the CNS both receptors are present but we concentrate more on nicotinic receptors.

Both receptors are excitatory (Ach excitatory everywhere)

-We said that the cortex contains only GABA and glutamate, but it receives modulators from all NT and one of these is Ach. Modulators come from areas other than the cortex and modulate the cortex's function and allow the cortex do more than one function. So any imbalance will result in a disorder. (don't memorize drugs and synapses of Ach).

-Ach sources : in the base of the brain we have **nucleus basalis** and we have some small nuclei present in the brain stem which also produce Ach.

- There are 2 pathways for Ach:

1) **Ventral pathway**: mainly will go to the cortex and activate it .

2) **Dorsal pathway**: go through thalamus to then to the cortex to activate it. Since they pass the thalamus they must have sensory related-functions such as enhancement of sensory perceptions , responsible for arousal and reward due to exciting the cortex, sustain attention and help in memory (doesn't have direct effect in memory production).

-The commonest disorder related to Ach pathway disturbances is **Alzheimer's disease** which results from loss of Ach neurons ( cholinergic cells ) in nucleus basalis .

- **Biogenic amines**

-Main neuromodulators, slow modulators .

- Include: norepinephrine / epinephrine / dopamine. All of them can be degraded by mono amine oxidase enzyme , mainly present in the CNS. Also they picked up transporters, so they are eliminated from synapses by both transporters and degradation ( memorize their synthesis steps ) .

- Tyrosine hydroxylase is the rate limiting enzyme .



- **Dopamine**

- All dopamine receptors are **G-protein** coupled receptors
- **We have 5 subfamilies of dopamine receptors :**
  - **D1+D5** ( excitatory ).
  - **D3+D2+D4** ( Inhibitory )
- D2 is the most important, it is presynaptic auto receptor and is inhibitory which means it can regulate the release and act as a break → negative feedback.

- Anything that affects the transporter such as cocaine or amphetamine will affect the dopamine also.  
And things that affect MAO also affect dopamine.

- **The sources of dopamine in the brain :**

- Substantia nigra in midbrain.
- Ventral tegmental area in midbrain

- **Dopamine has 3 pathways (to 3 targets):**

1. Cortex: prefrontal cortex → mesocortical . Distribution includes parietal and occipital lobes but mainly goes to the prefrontal cortex.
2. Limbic system: nucleus accumbens .
3. Striatum: basal ganglia

- If any disturbances that occur in any one of these pathways → that will result in the symptoms of disorders specific to that area ( target area ):

- if the target is striatum → there will be a problem in the basal ganglia → **Parkinson's disease**.
  - if the target is nucleus accumbens → there will be a problem in the nucleus accumbens and the limbic system → problem in emotions and reward → **Schizophrenia** (this occurs in cocaine addicts)
    - anything that helps release dopamine in the limbic system is addictive
    - Hallucinations = positive symptoms of schizophrenia
  - if the target is the prefrontal cortex → this cortex carries out the functions of planning personality and social interactions → so any disturbances will produce problem in this activity → **depression** → negative symptoms of schizophrenia .
- If we have a patient with positive symptoms of schizophrenia → we give him dopamine antagonist drugs → the patient will experience negative symptoms instead! Therefore we are searching for better drugs targeting more specific receptors.

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