This lecture contains two parts: the 1st one is about Neuropeptides and the second is about olfaction.

Neuropeptides:

proteins that are active as neurotransmitters. The most important are those which found in the hypothalamus to regulate the function of endocrine system. Its synthesis is in the short axon cell. All of them work through G protein coupled receptors, we will talk about ***Opioids***.

*There are three families of opioids:

- Enkephalins >> work through delta receptors
- Endorphins >> work through μ receptors
- Dynorphins >> work through kappa receptors

***Enkephalins** : work through delta receptors to inhibit or excite (depending on the type of receptor it acts on). One of the main functions of opioids is modulation of pain through periaqueductal grey pathway to Raphe nucleus to descend and go down in the spinal cord with the intermediate serotonin receptors to modulate and inhibit pain function.

- remember: to modulate the function of pain, to block pain from getting up to the brain and to stop feeling pain from periphery; we can block the ALS system at the level of the spinal cord. In this case one of the main pathways Is that we have opioid neurons (Enkephalins) that activate serotonin neurons that will descend through the spinal cord to activate another opioid neurons, to inhibit the transmitting of pain in the ALS and block it; in the synapses between pre and post synaptic in first and second order neurons.

And it can be trained; this is the way by which some people train themselves to walk on embers, by blocking pain sensation from getting to the brain.

***Dynorphins**: they are found in the spinal cord; modulate the function of sensation other than pain.

***Endorphins** : they are similar to *morphine* [which is not an endogenous NT, it is a natural product that works to suppress pain by acting on μ receptors, then they discovered that there must be an endogenous substances act on these receptors which are endorphins, these are produced internally by the brain and act on μ receptors] .

μ receptors spread in many areas of the brain, more than delta and kappa, mainly in the upper areas of CNS ,such as; thalamus, brain stem, hypothalamus, midbrain even the cortex . It can modulate not only the function of blocking pain from reaching the brain, but also how we interrupt pain and blocking the suffering part of it .

It also can induce blocking to the centers in the brain stem and hypothalamus that are responsible for internal regulation; such as respiration and temperature regulation, so it has side effects and at high levels can induce death.
Kappa is less distributed, only in few amounts in spinal cord and limbic system. So we usually neglect it.

Non-traditional NT:

We took previously that a NT is whatever molecule that can be packed in vesicles, released upon arrival of the AP, go to the postsynaptic receptor, bind and affect it.

If we have NTs that don't obey these criteria..>>we call them non classical /non-traditional ones.

A . Nitric oxide (NO) :

*Normally it is a gas, which can't be packed in a vesicle because it will diffuse out . So it should be produced upon needed. It is synthesized by nitric oxide synthase; an enzyme its activation is induced by calcium in the cytosol, the neuronal type is NOS-1.
[Increased calcium >>activation of calcium cascade >> activation of NO synthase >>production of NO that will diffuse and go to its receptors to do certain function] .

*in the brain, there is some types of neurons that have certain types of NO synthase , produce NO (upon increase in calcium) that will diffuse and go to the neurons that have receptors for it, inducing calcium in these neurons .

*its main functions:

Because it induces calcium …>> it is a vasodilator on non neurons (regulate the amount of blood reaching certain areas).

Work on neurons to induce calcium, esp. for memory. Although NO is good for blood and memory but if it exceeds a certain limit it becomes neurotoxic, like the glutamate.

* It is associated with glutamate induced neurotoxicity / Stroke:
If we have ischemia >>this will kill neurons by cytotoxicity [glutamate bound to its receptors >>induce calcium>> >>drive cell toward apoptosis],and all the neurons in that area will die even the ones that don't have glutamate receptors and the activity of NOS and the deficit might be increased, Why ?

Neurons has NMDA R ,it is overactive and opened in stroke → increase Ca+ → then at a certain level Ca+ activate NOS → produce and diffuse NO in high amount → it will go to neighboring neurons (even if it wasn't ischemic) → increase calcium there and eventually drive cells toward apoptosis.

B . Brain derived neurotrophic factor [BDNF] :

It is considered a non-traditional one, not only because it acts through tyrosine kinase receptor that will activate tyrosine kinases, which induce functions in the cell, but because it mainly works through postsynaptic to presynaptic, its receptor is found on the presynaptic, and it is not an autoreceptor,[because it is secreted from postsynaptic despite it is found on presynaptic] >> this errs the theory which says that synapses are one directional.

*remember that the end function of tyrosine kinases is cell survival and growth. The signal is at the end of the cell, while the survival and growth mainly initiated in the cell body. So the signal should be transmitted to the cell body… how this occurs??

When BDNF binds to its receptor, this complex will be packed into a vesicle that will be transported back through the axon to the cell body, and there they will do their function by inducing living and growth.

One of the experiments done on this topic is bringing neurons, putting cell bodies in an area/chamber and the axon terminals in another one, then we bring a neuronal growth factor – one of them is BDNF. If we put them in the cell bodies, they will not survive, but if in axons we will detect them in the cell bodies and they induce survival.

→Remember the general principle here in simple words; that what work will survive and what doesn't work will die end be eliminated. So, each neuron survival and function depends on the neuron previous to it (because it delivers the AP), so the neuron sends BDNF to it (the previous neuron) and both survive.

*It is important during the development in early life, to make a good shape and communication of the CNS. (In early life the SMA communicates with the whole brain and during activity and experience there will be elimination for unneeded/unwanted neurons, this is done by BDNF and other neuronal growth factors.)

But also it is important in adults' life, because as what we know that neurons number will not increase but the complexity of the axons and dendrites increase/decrease depending on the experience, esp. for memory.

We have different subtypes of memory:

1) Declarative >> which is available to consciousness.
   It includes the answers for any question [what is ur name , in which

university ….etc.]. Giving you fast answers and explanations. it has special site in the brain , stored in the cortex

2) Non declarative >>which is not available to consciousness
   Here we remember things not related to questions.
   Motor skills, puzzle solving skills ……
   Not stored in the cortex.

*how does memory occur ???

We have an internal signal >> induce it to a circuit in the brain, it keeps rotating as long as we use it, this is a working or short term memory. In long term memory

This circuit will be converted from non permanent (just a signal) to a permanent circuit; this electrophysiological conversion must be associated with anatomical one, which is called long term potentiation [LTP] or long term depression [LTD].

***Long term potentiation** : if we have a presynaptic neuron with an induced AP ,this leads to release of NT that will go to the postsynaptic neuron, here the membrane potential may reach the threshold>>so generating AP , or won't reach the threshold >> no AP .

In this case if we have two neurons, the first doesn't induce an AP on the second one [only sub threshold excitatory postsynaptic potentials-EPSP-]this is normal. if the first one acts on multifrequency which results in summation of these EPSP>>generating AP on the second neuron . Now the second neuron is active and will do its function, it will send BDNF to the first one to induce its growth and strengthen the relation between them. [How it is strengthened physiologically?? If the same AP that previously made sub threshold on postsynaptic neuron, comes now after potentiation , it will induce AP on the postsynaptic one].

Potentiation>> a permanent relation is built between the two neurons.

***long term depression**: if the synapses between the two neurons were inhibitory, such as in the cerebellum.

*how this process is expressed anatomically ??

The neuron has received BDNF >>induce growth and survival. Growth is by sending more collaterals of axons, more axon terminals, the axon terminals get bigger. These can be stained and seen under anatomical microscope >> we call them spines [interaction sites or synapses].

Notice the difference between the dendrites in the pictures in the slides .

NOTE: here you should differentiate between division and development of neurons!

They don't divide, they only develop by sending more collaterals and terminals [axons and dendrites], getting thicker and having more NTs , but there is no effects on the cell body .

*So all these are involved in memory formation at the cellular level, also calcium at a certain level is good, induces growth and survival. So NTs acting through calcium are usually associated with memory formation in the brain.

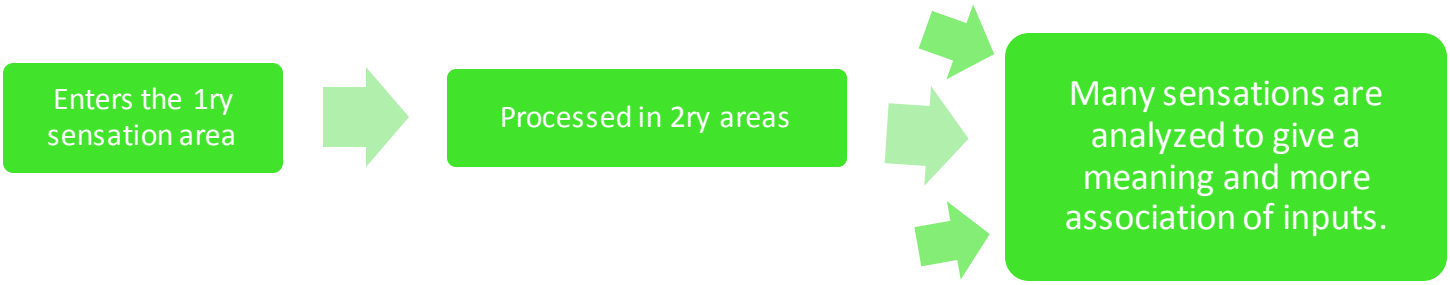
THE CHEMICAL SENSES:

OLFACTION AND GUSTATION

SENSATION IN THE CORTEX

When sensations eventually reach the cortex, they are processed. Thereof, the cortex was divided by the physiological function into primary, secondary and association cortex. The primary cortex in sensation is the first area that receives the sensation (*from* thalamus) and in the motor is the one that directly communicates with the motor. When the sensation arrives, it enters through the thalamus into the primary cortical area where it is detected, and then analyzed for a meaning.

- So first any sensation enters the primary area then gets processed in the secondary areas, after that all this information must be integrated to give a complex meaning, thoughts and higher functions in the association cortex which has areas that have more than one modality of sensation which usually form the higher functions.
- In brief, the following diagram illustrates the route of sensations going to the brain:



GENERAL TERMS: APRAXIA AND AGNOSIA

- Apraxia is the inability to perform complex movements although there is no paralysis in any muscle.

In apraxia, the premotor and the supplementary were damaged/defected which correspond to secondary motor cortex. Premotor is called premotor because the secondary areas in motor do the processing first then the movement occurs unlike in the case of sensation where the sensation first arrives then it gets processed. So after a damage to the secondary motor cortex, the person still can move but they cannot 'make' a meaning for that move (there is no complex movement to perform a designated task).

Same principle applies to the sensation: If the 'tract' of the sensation or the primary area was damaged, there will be a loss of sensation. But if the secondary areas of sensation were damaged, there will not be a meaning for that sensation. This is termed ***agnosia***. For example, if the olfactory area was damaged -> olfactory agnosia. Visual area -> visual agnosia. Auditory area -> auditory agnosia. Sometimes a submodality of a certain area can be damaged as in the case of damaging the part that recognizes trees in the visual area -> tree agnosia (shape). Color -> color agnosia and so on. *So agnosia is a general term that literally means 'I cannot recognize or interpret that sensation in that particular meaning.* The defect can be either in the secondary or association areas.

THE OLFACTORY SYSTEM

Olfaction is the ability to smell. The olfactory system starts in the nasal cavity, the nasal epithelium in the nasal cavity or olfactory epithelium. The olfactory epithelium is constituted of three main cell types, which are:

1. *Receptors*: olfactory receptor neurons, almost bipolar type of cells. The first pole has *cilia* with receptors on them and the other sends sensory fibers. Their function is to detect the chemical signals and transfer it into electrical signals.
   - The neurons cannot live by themselves so they need support and this is the function of the next type.
2. *Supporting* cells: the columnar epithelial cells which provides mechanical, chemical, environmental and food support to the neurons.
   - Those are exposed to the external environment therefore the neurons die and renew themselves in a continuous process every one to three months; this is the function of the next cell type.
3. *Basal cells*: which are undifferentiated cells that are responsible for the regeneration of both the neuronal and supporting cells.

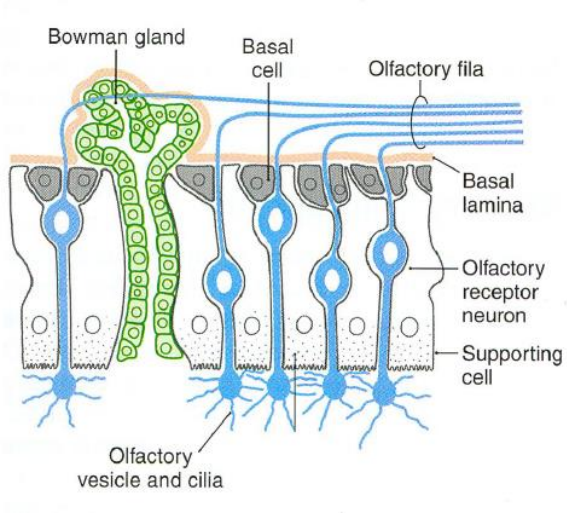


Figure 1: The olfactory epithelium

THE PROCESS OF OLFACTION

It is a chemical sensation wherein chemicals should bind to receptors so the chemicals must be dissolved in a media, and this is the function of the Bowman cells/glands; first it secretes fluid to dissolve the chemical substances then some mucus for lubrication and protection of microbial infections or whatever.

Next, the receptors in the neurons will send the axons centrally and enter the skull through the *cribriform* plate (which is in the roof of the nasal cavity and has many pores through which the axons could pass) and there on the plate they will synapse with the second-order neurons in the *olfactory bulb*. The olfactory bulb is the enlargement at the ending of the olfactory nerve and tract. Also in the synapse, there is come processing in that enlargement.

The connection between the first-order neurons (i.e. the receptors) and the second-order neurons (i.e. the olfactory bulb neurons) does not happen as one-to-one connection, rather, in a magnificent gathering/collection known as ***glomeruli*** or a glomerulus as single. In the glomeruli, there is convergence and divergence where three or four receptors will gather at one neuron (convergence) or a single neuron sending to more than one neuron (divergence). All those help in processing of olfaction even at the level of the olfactory bulb.

Note that all receptors of chemical sensation work through 2nd-messenger type of receptors. One of the most important characteristics of the 2nd-messenger signal is that it gives complex response not only opening or closing of a channel but also affecting proteins, structures and the most important being the *signal amplification*. It is way more potent because it amplifies the signal, which allows detection of lower thresholds of sensations since it is going to be amplified.

Humans smell thousands of odors. However, it is impossible to have thousands of classes of receptors. There could be one hundred classes of receptors and the reason of smelling thousands is *because of the glomeruli, its distribution and the mixing.* So mixing will allow identification of more odors. Also notice that in many of the special sensations and mainly in the olfaction and vision, there are cells whose function is to extend themselves horizontally between the glomeruli and the connections and this helps more and more in processing. (Horizontal red cells in **figure 2**)

The last function in the olfactory bulb is *adaptation*. **Consider this**: if you enter a flower shop for example, you first smell strong scents then after two minutes you no longer smell anything, this is adaptation. There are many levels of adaptation; on the receptor itself, it binds a chemical substance -> gets activated -> the cell then blocks it by adding or removing cAMP or internalization et cetera…

Now **consider this**: you sprayed some perfume in the morning, you smelled it for a minute then it is gone. Then you met someone who admired your perfume and so you started to smell it again. What is the explanation?

- A: Olfactory adaption occurs at the level of receptors, this is one part. But the other part and the main adaption which helps in processing and adaption together is some fibers coming from the olfactory cortex to the olfactory bulb and there it will induce either inhibition or stimulation of the glomeruli at the second-order neurons. Inhibition when there is adaption and *stimulation in case of processing*. This is the function of the centrifugal fibers shown in **Figure 2**.

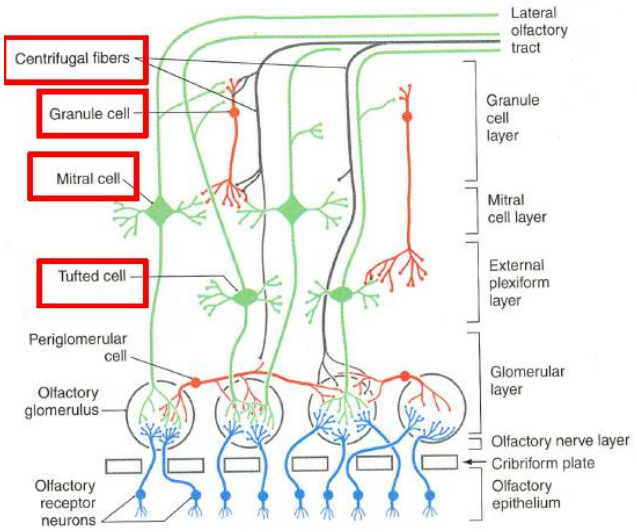


Figure 2: Notice the following: 1) The red horizontal cells which help in more mixing and processing. 2) The centrifugal fibers which help in processing and adaptation.

- So in the end, we can differentiate between smells because of the presence of many subclasses of receptors and different combinations in the glomeruli which make different transduction mechanisms reaching the second-order neurons in red and green as in **Figure 2** where processing, inhibition and centrifugation occur.

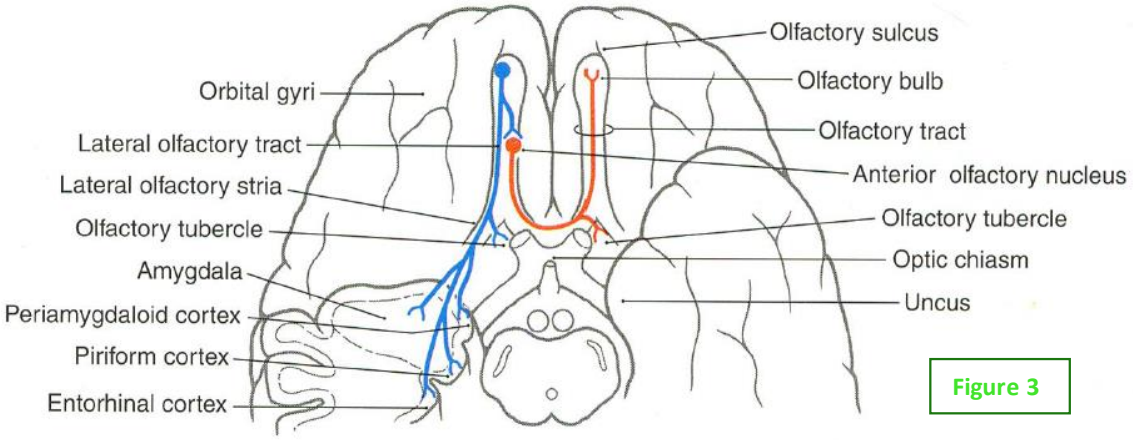


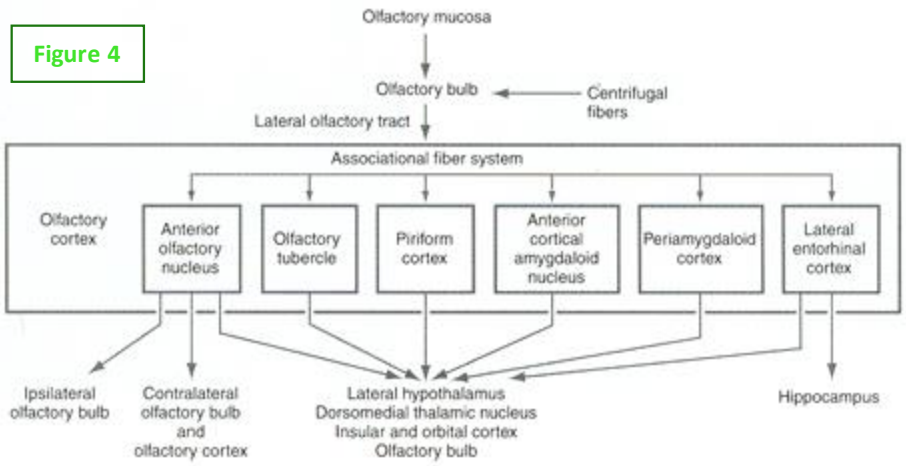
Figure 3

- (Continuing with the sensation route, **figure 3**) After that, from the olfactory bulb, the sensation goes to the olfactory tract to the central areas where it divides into two pathways: the 1) *medial part* usually synapses in the middle of the tract over something called the anterior olfactory nucleus, its function is to *make the processing at the olfactory bulb* and do the crossing and connection between the two sites (at the level of the olfactory bulb and the bulb-cortex). Most of its fibers' target is either to the *second* olfactory bulb or ipsilateral olfactory bulb and a few to the cortex. 2) The *lateral part/tract* keeps going from the olfactory bulb directly to the central areas.

In the ALS pathway, there was 'something' that goes to the cortex, through thalamus to the cortex to provide perception of the ALS modalities. There was also another 'something' that stops at the brainstem then to the hypothalamus and to other numerous places.

Accordingly, the one that will enter the cortex will follow the rule of neocortex-through-thalamus while the other does not target the neocortex - sometimes the target is the paleocortex as in the limbic system which should not pass through the thalamus-. The same principle applies here, *two thirds* of the lateral tract and the olfactory system will pass through the thalamus and from the thalamus to the neocortical areas and this is very important for giving meaning and processing of olfaction. While *the other third* will go to the other areas that are associated with reflexes of olfaction (smelling food makes you hungry), internal regulation, emotion, feeding, hunger, hypothalamus, anger, emotions like amygdaloid and some old cortices that are associated with primitive processes and functioning (paleocortex). The old cortices are olfactory tubercle, piriform cortex, anterior amygdaloid, periamygdaloid and entorhinal cortex, this is the first third. While the other two thirds will go to the dorsomedial thalamus then to the olfactory cortex that is nearly in the same area on the medial and inferior part of the temporal lobes, (**figure 4**.)

Figure 4



Now, for more processing, the sensation will go to the secondary cortex and from there to the multimodal cortex that is the association cortex. One of the most important areas of secondary cortices (also has a slight relation with the association cortex) is the orbitofrontal cortex. From there it provides the meaning of the olfactory sensation especially the right side (which is more important than the left side.) So if the right side is gone, the person can smell but cannot know what exactly they smell. Reflexes may get affected.

If the tract was damaged, there will be a loss of sensation and this called anosmia or hyposmia whether complete or partial loss. The most common cause is that the chemicals did not bind to the receptors and this happens in case of edema, inflammation of the nasal cavity, cold or flu, sinusitis... A cut in the tract can occur due to a trauma, mostly a trauma to the face, the first and the most famous part to be broken is the cribriform plate that will cut the first order neurons axons -> anosmia. In the case of a little cut or no inflammation, basal cells will regenerate and the axon will reach its destination again (temporary loss of sensation). But in case of inflammation, inflammation damages the 'guidance queue' so no correction can take place -> forever loss.

Other degenerative diseases like Huntington's or Alzheimer's have continuous loss of sensation especially the olfactory. You are required to read them from the following references:

- *Disorders of the Olfactory System (page 704-707),*
- *Disorders of the Gustatory System (page 716)*