# Neuron types and Neurotransmitters

#### Faisal I. Mohammed. PhD, MD



## Objectives

- Understand synaptic transmission
- List types of sensory neurons
- Classify neurotransmitters
- Explain the mechanism of neurotransmission
- Judge the types of receptors for the neurotrasmitters

### Functional Unit (Neuron)



# Transmission of Receptor Information to the Brain

- The larger the nerve fiber diameter the faster the rate of transmission of the signal
- Velocity of transmission can be as fast as 120 m/sec or as slow as 0.5 m/sec
- >Nerve fiber classification
  - type A myelinated fibers of varying sizes, generally fast transmission speed
    - > subdivided into  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$
    - type B- partially myelinated neurons (3-14m/sec speed)
    - type C unmyelinated fibers, small with slow transmission speed



0.5

Tickle

0.5

0.5

#### **Neuron Classification**



### Structural Classification of Neurons



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#### Neurotransmitters

Chemical substances that function as synaptic transmitters

- 1. Small molecules which act as rapidly acting transmitters
  - acetylcholine, norepinephrine, dopamine, serotonin, GABA, glycine, glutamate, NO
- 2. Neuropeptides (Neuromodulators)
  - more potent than small molecule transmitters, cause more prolonged actions
  - endorphins, enkephalins, VIP, ect.
  - hypothalamic releasing hormones
  - TRH, LHRH, ect.
  - pituitary peptides
  - ACTH, prolactin, vasopressin, ect.

# Neurotransmitters

#### Table 45–1

#### Small-Molecule, Rapidly Acting Transmitters

Class I Acetylcholine Class II: The Amines Norepinephrine Epinephrine Dopamine Serotonin Histamine Class III: Amino Acids Gamma-aminobutyric acid (GABA) Glycine Glutamate Aspartate Class IV Nitric oxide (NO)

#### Table 45-2

Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones Thyrotropin-releasing hormone Luteinizing hormone-releasing hormone Somatostatin (growth hormone inhibitory factor) Pituitary peptides Adrenocorticotropic hormone (ACTH) β-Endorphin α-Melanocyte-stimulating hormone Prolactin Luteinizing hormone Thyrotropin Growth hormone Vasopressin Oxytocin Peptides that act on gut and brain Leucine enkephalin Methionine enkephalin Substance P Gastrin Cholecystokinin Vasoactive intestinal polypeptide (VIP) Nerve growth factor Brain-derived neurotropic factor Neurotensin Insulin Glucagon From other tissues Angiotensin II Bradykinin Carnosine Sleep peptides Calcitonin



# Comparison between Small Molecules and Neuropeptides Neurotramsmitters (NT)

- Small molecules NT are rapidly acting as compared to slowly acting neuropepides
- Neuron has only one NT but may have one or more NP
- Small molecules NT are have short lived action compared to prolonged time of action for neuropeptides
- Small molecules NT are excreted in larger amounts compared to smaller quantities of neuropeptide
- Small molecules NT vesicles are recycled but neuropeptide ones are not
- Neuropeptides are co-secreted with small molecules NT
- Neuropeptides are synthesized at the soma while small molecules could be formed at the presynaptic terminals

## **Removal of Neurotransmitter**

#### Diffusion

move down concentration gradient Enzymatic degradation Acetylcholinesterase for (Ach), peptidases for neuropeptides Uptake by neurons or glia cells neurotransmitter transporters Prozac = serotonin reuptake inhibitor



Neurotransmitter can be recycled in presynaptic terminal or can be broken down by enzymes within the cell

#### II Neurotransmitters and receptors

#### **Basic Concepts of NT and receptor**

Neurotransmitter: Endogenous signaling molecules that alter the behaviour of neurons or effector cells.

Neuroreceptor: Proteins on the cell membrane or in the cytoplasm that could bind with specific neurotransmitters and alter the behavior of neurons of effector cells •Vast array of molecules serve as neurotransmitters

•The properties of the transmitter do <u>not</u> determine its effects on the postsynaptic cells

•The properties of the **receptor** determine whether a transmitter is excitatory or inhibitory

#### A neurotransmitter must (classical definition)

- Be synthesized and released from neurons
- Be found at the presynaptic terminal
- Have same effect on target cell when applied externally
- Be blocked by same drugs that block synaptic transmission
- Be removed in a specific way





A substance that mimics a specific neurotransmitter,

is able to attach to that neurotransmitter's receptor

and thereby produces the same action that the neurotransmitter usually produces.

Drugs are often designed as receptor agonists to treat a variety of diseases and disorders when the original chemical substance is missing or depleted.

#### Antagonist

Drugs that bind to but do not activate neuroreceptors,

thereby blocking the actions of neurotransmitters or the neuroreceptor agonists.

- Same NT can bind to different -R
- different part of NT ~





#### Five key steps in neurotransmission

- Synthesis
- Storage
- Release
- Receptor Binding
- Inactivation



## **Synaptic vesicles**



- Concentrate and protect transmitter
- Can be docked at active zone
- Differ for classical transmitters (small, clear-core) vs.
  neuropeptides (large, dense-core)

# Neurotransmitter Co-existence (Dale principle)

Some neurons in both the PNS and CNS produce both a classical neurotransmitter (ACh or a catecholamine) and a polypeptide neurotransmitter.

They are contained in different synaptic vesicles that can be distinguished using the electron microscope.

The neuron can thus release either the classical neurotransmitter or the polypeptide neurotransmitter under different conditions.

Neuropeptide Small-molecule in large dense-core vesicles neurotransmitter in small clearcore vesicles Localized increase in Ca2+ concentration Low-frequency stimulation  $\bigcirc$ Preferential release of small- $\bigcirc$ molecule neurotransmitter More diffuse increase in Ca2+ concentration High-frequency stimulation Release of both types of transmitter

### Receptors determine whether:

- Synapse is excitatory or inhibitory
  - NE is excitatory at some synapses, inhibitory at others
- Transmitter binding activates ion channel directly or indirectly.
  - Directly
    - ionotropic receptors
    - fast
  - Indirectly
    - metabotropic receptors
    - G-protein coupled
    - slow

#### **Receptor Activation**

- Ionotropic channel
  - directly controls channel
  - fast
- Metabotropic channel
  - second messenger systems
  - receptor indirectly controls channel ~



### **Ionotropic Channels**



#### **Ionotropic Channels**



#### **Ionotropic Channels**



#### Metabotropic Channels

- Receptor separate from channel
- G proteins
- 2nd messenger system
  - cAMP
  - other types
- Effects
  - Control channel
  - Alter properties of receptors
  - regulation of gene expression ~

#### G protein: direct control

- NT is 1st messenger
- G protein binds to channel
  - opens or closes
  - relatively fast ~







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# **Transmitter Inactivation**

- Reuptake by presynaptic terminal
- Uptake by glial cells
- Enzymatic degradation
- Presynaptic receptor
- Diffusion
- Combination of above



### Summary of Synaptic Transmission

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#### Purves,2001 40



# Some Important Transmitters

### (1) Acetylcholine (ACh) as NT



## Acetylcholinesterase (AChE)

- Enzyme that inactivates ACh.
  Present on postsynaptic membrane or immediately outside
  - the membrane.
- Prevents continued stimulation.

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# Ach - Distribution

#### **Peripheral N.S.**

- Excites somatic skeletal muscle (neuro-muscular junction)
- Autonomic NS

Ganglia

Parasympathetic NS--- Neuroeffector junction

Few sympathetic NS – Neuroeffector junction

Central N.S. - widespread

Hippocampus Hypothalamus ~

# Ach Receptors

•ACh is both an excitatory and inhibitory NT, depending on organ involved.

-Causes the opening of chemical gated ion channels.

#### •Nicotinic ACh receptors:

–Found in autonomic ganglia  $(N_1)$  and skeletal muscle fibers  $(N_2)$ .

#### •Muscarinic ACh receptors:

–Found in the plasma membrane of smooth and cardiac muscle cells, and in cells of particular glands .

# Acetylcholine Neurotransmission

- <u>"Nicotinic" subtype Receptor:</u>
  - Membrane Channel for  $Na^+$  and  $K^+$
  - Opens on ligand binding
  - Depolarization of target (neuron, muscle)
  - Stimulated by Nicotine, etc.
  - -Blocked by Curare, etc.
  - -Motor endplate (somatic)  $(N_2)$ ,
  - all autonomic ganglia, hormone producing cells of adrenal medulla (N<sub>1</sub>)

# Acetylcholine Neurotransmission

- <u>"Muscarinic" subtype Receptor: M</u><sub>1</sub>
  - Use of signal transduction system
    - Phospholipase C, IP<sub>3</sub>, DAG, cytosolic Ca<sup>++</sup>
  - Effect on target: cell specific (heart ↓, smooth muscle intestine ↑)
  - Blocked by Atropine, etc.
  - All parasympathetic target organs
  - Some <u>sympathetic</u> targets (endocrine sweat glands, skeletal muscle blood vessels dilation)

# Acetylcholine Neurotransmission

#### • "Muscarinic" subtype: M<sub>2</sub>

– Use of signal transduction system

- via G-proteins, opens K<sup>+</sup> channels, decrease in cAMP levels
- Effect on target: cell specific
- CNS
- Stimulated by ?
- Blocked by Atropine, etc.

# Cholinergic Agonists

- Direct
  - Muscarine
  - Nicotine
- Indirect
  - AChE Inhibitors ~

# Cholinergic Antagonists

• Direct

Nicotinic - Curare Muscarinic - Atropine

# **Ligand-Operated ACh Channels**







(Purves D, Augustine GJ, Fitzpatrick D, Neuroscience, 2nd ed. Sunderland, MA, Sinaver Associates, 2001.)

### Neurotransmitter "Second Messenger" System



### **G** Protein-Operated ACh Channel

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#### M receptor



# (2) Monoamines as NT

# Monoamines

Catecholamines –
Dopamine - DA
Norepinephrine - NE
Epinephrine - E

• Indolamines -

Serotonin - 5-HT



#### Mechanism of Action (β receptor)

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# Norepinephrine (NE) as NT

- NT in both PNS and CNS.
- PNS:
  - Smooth muscles, cardiac muscle and glands.
    - Increase in blood pressure, constriction of arteries.
- CNS:
  - General behavior.



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#### $\alpha_1$ Receptor

- Stimulated by NE, E,
- blood vessels of skin, mucosa, abdominal viscera, kidneys, salivary glands
- vasoconstriction, sphincter constriction, pupil dilation

#### $\alpha_2$ Receptor

- stimulated by, NE, E, .....
- Membrane of adrenergic axon terminals (presynaptic receptors), platelets
- inhibition of NE release (autoreceptor),
- promotes blood clotting, pancreas decreased insulin secretion

#### $\beta_1$ receptor

- stimulated by E, ....
- Mainly heart muscle cells,
- increased heart rate and strength

- $\beta_2$  receptor
  - stimulated by E ..
  - Lungs, most other sympathetic organs, blood vessels serving the heart (coronary vessels),
  - dilation of bronchioles & blood vessels (coronary vessels), relaxation of smooth muscle in GI tract and pregnant uterus

#### • $\beta_3$ receptor

- stimulated by E, ....
- Adipose tissue,
- stimulation of lipolysis

## (3) Amino Acids as NT

- Glutamate acid and aspartate acid: –Excitatory Amino Acid (EAA)
- Gamma-amino-butyric acid (GABA) and glycine:
  - –Inhibitory AA

# (4) Polypeptides as NT

- CCK: (cholecystokinin)
  - Promote satiety following meals.
- Substance P:
  - Major NT in sensations of pain.
## (5) Monoxide Gas: NO and CO

- Nitric Oxide (NO)
  - Exerts its effects by stimulation of cGMP.
  - Involved in memory and learning.
  - Smooth muscle relaxation.
- Carbon monoxide (CO):
  - Stimulate production of cGMP within neurons.
  - Promotes odor adaptation in olfactory neurons.
  - May be involved in neuroendocrine regulation in hypothalamus.



## Sensory Receptors; Neuronal Circuits For Processing Information

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## Objectives

- Define receptors (Transducers) and classify them
- Describe the generator (receptor) potential and its importance in sensory coding
- List the types of somatic receptors in the skin
- Explain the mechanism of sensory coding
- Interpret the mechanism of receptor adaptation and classify the types of receptors accordingly (Phasic and Tonic receptors)
- Describe sensory neuronal processing and its functional importance

## Types of Sensory Receptors: Classification by Modality (Stimulus they transduce)

- Mechanoreceptors
  - detect deformation, Touch and Prssure
- > Thermoreceptors
  - detect change in temperature
- Nociceptors
  - detect tissue damage (pain receptors)
- Electromagnetic (Photoreceptors)
  - detect light (Rods and Cones)
- Chemoreceptors
  - $\succ$  taste, smell, CO<sub>2</sub>, O<sub>2</sub>, etc.

## Classification by Location

- Exteroceptors sensitive to stimuli arising from outside the body
  - Located at or near body surfaces
  - Include receptors for touch, pressure, pain, and temperature
- Interoceptors (visceroceptors) receive stimuli from internal viscera
  - Monitor a variety of stimuli (distension of viscera, pain)
- Proprioceptors sense of position- monitor degree of stretch
  - Located in musculoskeletal organs (muscle, tendons and skin around joints)

## Types of Sensory Receptors



apparatus



Tactile hair



Krause's corpuscle



Muscle spindle





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#### Merckel's disc for mechanical sensation (Touch in hairy skin)



# Iggo dome receptors

#### Figure 47–1

Iggo dome receptor. Note the multiple numbers of Merkel's discs connecting to a single large myelinated fiber and abutting tightly the undersurface of the epithelium. (From Iggo A, Mult AR: The structure and function of a slowly adapting touch corpuscie in hairy skin. J Physiol 200: 763, 1969.)

## **Tactile Receptors**

- Free nerve endings (A $\delta$  and C fibers)
  - detect touch and pressure
  - found everywhere in the skin and other tissues
- Meissner's corpuscles  $(A\beta)$ 
  - rapidly adapting (within a fraction of a second) and detect movement of light objects over skin
  - found on nonhairy skin (glabrous skin), fingertips and lips
- Merkel's discs  $(A\beta)$ 
  - respond rapidly at first and then slowly adapt, detect the "steady state"
  - found on hairy as well a glabrous (non hairy) skin

## **Tactile Receptors**

- Hair end organ
  - adapts rapidly and detects movement over the body
- Ruffini's end organ
  - slowly adapting and respond to continual deformation of the skin and joint rotation
- Pacinian corpuscle
  - very rapidly adapting and is stimulated only by rapid movement
  - detects vibration and other rapid changes in the skin

## Tactile Sense Transmission

- Meissner's corpuscles, hair receptors, Pacinian corpuscles and Ruffini's end organs transmit signals in type Aβ nerve fibers at 30-70 m/sec.
- Free nerve endings transmit signals in type
  Aδ nerve fibers at 5-30 m/sec, some by
  type C unmyelinated fibers at 0.5-2 m/sec.
- The more critical the information the faster the rate of transmission.

#### Sensory Receptors: General structure

Receptor area is None-excitable region so as it can discriminate different intensities, otherwise it will not be able to differentiate strengths of stimuli



Conversion of Receptor and Generator Potentials into Action Potentials

#### **Receptor Potential**

#### **Generator Potential**





## Law of Specific Nerve Energies

- Sensation characteristic of each sensory neuron is that produced by its normal or adequate stimulus.
- □ Adequate stimulus:
  - Requires least amount of energy to activate a receptor.
- Regardless of how a sensory neuron is stimulated, only one sensory modality will be perceived (specificity of receptors)
  - Allows brain to perceive the stimulus accurately under normal conditions.

## Sensation

- Each of the principle types sensation; touch, pain, sight, sound, is called a *modality of sensation*.
- Each receptor is responsive to one type of stimulus energy. Specificity is a key property of a receptor, it underlines the most important coding mechanism, *the labeled line principle*
- How the sensation is perceived is determined by the characteristics of the receptor and the central connections of the axon connected to the receptor.

## **Receptor Excitation**

- mechanical deformation which stretches the membrane and opens ion channels
- application of chemicals which also opens ion channels
- change in temperature which alters the permeability of the membrane through changing the metabolic rate
- electromagnetic radiation that changes the membrane characteristics

## General Structure of Receptors



#### **Receptor Excitation**



## **Receptor Potential**

- > The membrane potential of the receptor
  - Excitation of the receptor results from a change in this potential.
  - When the receptor potential rises above the threshold, action potentials appear and the receptor is active.
  - The greater the intensity of the stimulus, the greater the receptor potential, and the greater the rate of action potential generation.

#### **Generator Potentials**

- In response to stimulus, sensory nerve endings produce a local graded change in membrane potential.
- Potential changes are called receptor or generator potential.
  - Analogous to EPSPs.



#### **Relationship between Receptor Potential and Action Potentials**



# The effect of stimulus strength on RP amplitude



## The effect of the amplitude of RP on the frequency of impulses generated



## Adaptation of Receptors

When a continuous stimulus is applied, receptors respond rapidly at first, but response declines until all receptors stop firing.



## Adaptation

- > Rate of adaptation varies with type of receptor.
- Therefore, receptors respond when a change is taking place (i.e., think of the feel of clothing on your skin.)

## Adaptation of Sensory Receptors

- Receptors responding to pressure, touch, and smell adapt quickly
- Receptors responding slowly include Merkel's discs, Ruffini's corpuscles, and interoceptors that respond to chemical levels in the blood
- Pain receptors and proprioceptors do not exhibit adaptation

## Slowly Adapting (Tonic) Receptors

- continue to transmit impulses to the brain for long periods of time while the stimulus is present
- keep brain apprised of the status of the body with respect to its surroundings
- will adapt to extinction as long as the stimulus is present, however, this may take hours or days
- these receptors include: muscle spindle, golgi tendon apparatus, Ruffini's endings, Merkels discs, Macula, chemo- and baroreceptors

### **Sensory Adaptation**

- □ Tonic receptors:
  - Produce constant rate of firing as long as stimulus is applied.
    - □ Pain.
- □ Phasic receptors:
  - Burst of activity but quickly reduce firing rate (adapt) if stimulus maintained.
  - Sensory adaptation:
    - Cease to pay attention to constant stimuli.



## Rapidly Adapting (Phasic) Receptors

- respond only when change is taking place
- Rate and Strength of the response is related to the Rate and Intensity of the stimulus
- important for predicting the future position or condition of the body
- very important for balance and movement
- types of rapidly adapting receptors: pacinian corpuscle, semicircular canals in the inner ear

## Importance of Signal Intensity

- Signal intensity is critical for interpretation of the signal by the brain (i.e., pain).
- ➢ Gradations in signal intensity can be achieved by:
- 1) increasing the number of fibers stimulated, spatial summation
- 2) increasing the rate of firing in a limited number of fibers, temporal summation.



## An example of spatial summation

## Coding in the sensory system

- □ Intensity is coded for by:
  - Frequency of action potential
  - The No. of neurons stimulated
- Location is coded for by the labeled line principles
- Type of stimulus is coded for by the kind of receptor stimulated (Adequate stimulus) and specificity of the receptors.

#### Coding of Sensory Information

-	STIMULUS PROPERTY	MECHANISM OF CODING
	Type of Stimulus (stimulus modality)	Distinguished by the type of receptor activated and the specific pathway over which this informa- tion is transmitted to a particular area of the cerebral cortex
	Location of Stimulus	Distinguished by the location of the activated receptive field and the pathway that is subsequently activated to transmit this informa- tion to the area of the somato- sensory cortex representing that particular location
	Intensity of Stimulus (stimulus strength)	Distinguished by the frequency of action potentials initiated in an activated afferent neuron and the number of receptors (and afferent neurons) activated



(a) Frontal section of primary somatosensory area in right cerebral hemisphere

#### Mapping of the Primary Somatosensory Area

Mapping of the postcentral gyrus. Size of the cortical region representing a body part depends on density of receptors on that part and the sensory impulses received from that part.

Figure 16.08 Tortora - PAP 12/e Copyright © John Wiley and Sons, Inc. All rights reserved.
#### **Receptive Fields**

- □ Area of skin whose stimulation results in changes in the firing rate of the neuron.
  - Area of each receptor field varies inversely with the density of receptors in the region.
- □ Back and legs have few sensory endings.
  - Receptive field is large.
- □ Fingertips have large # of cutaneous receptors.
  - Receptive field is small.



# An example of spatial summation

#### **Two-Point Touch Threshold**

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## Neuronal Processing

# Relaying Signals through Neuronal Pools



### Neuronal Pools

- groups of neurons with special characteristics of organization
- comprise many different types of neuronal circuits
  - converging
  - > diverging
  - reverberating

### **Neuronal Pools: Localization of sensory Information modification**



#### **Convergence and Divergence**



#### **Neuronal Pools: Modification of Localization: Sharpening of signals**



#### Lateral inhibition

#### **Lateral Inhibition**

- □ Sharpening of sensation.
  - When a blunt object touches the skin, sensory neurons in the center areas are stimulated more than neighboring fields.
  - Stimulation will gradually diminish from the point of greatest contact, without a clear, sharp boundary.
    - Will be perceived as a single touch with well defined borders.

Occurs within CNS.



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Lateral Inhibition in the sensory System as a way of sharpening of the stimulus



#### **Reverberating Circuits: prolongation of Time of the signals**



### **The Organization of Neuronal Pools**



# **Types of Circuits in Neuronal Pools**



# Neural Circuits



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# Other mechanisms for prolongation of time

- Synaptic afterdischarge: since the time of EPSP (15-20 msec) is longer than the time of AP(0.1 – 10 msec) then more No. of AP per one EPSP
- Parallel circuits

# Stabilization of neuronal discharge

- Synaptic fatigue: short term and acute adjustment of sensitivity
- □ Neuronal inhibitory circuits:
  - Gross inhibition –Basal ganglia inhibits muscle tone
  - Feed back inhibition-Cortico-fugal fibers from cerebral cortex descending fibers to control the intensity and sharpness
- Downregulation and upregulation- Long term stabilization through modification of the receptor availability (internalization or externalization)

