

# PSYCHO-PHARMACOLOGY

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## COURSE OBJECTIVES

- Ø Describe general principles of psychopharmacology
- Ø Mention classifications, potency and efficacy of anti-depressants, antipsychotics, anti-cholinergics and mood stabilizers.
- Ø Define the mechanisms of therapeutic effects of psychotropic drugs
- Ø Identify the different types of psychotropic drugs and their indications
- Ø List therapeutic indications of each class of drugs

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## Introduction

- u Concept of neurotransmitters
- u What are the basic facts about metabolism?
- u How CYP-based DDIs occur?
- u What are the CYP substrates, inhibitors and inducers and genetic factors?
- u How to prevent possible DDIs occurs?

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## Introduction cont'd...

### Anatomical versus chemical basis of neurotransmission

What is neurotransmission?

- ⌚ Neurotransmission can be described in many ways: **anatomically, chemically, electrically.**
- ⌚ **The anatomical basis** :-neurons and the connections between them, called synapses ;
- ⌚ also called the **anatomically addressed nervous system.**
- ⌚ Synapses can form on many parts of a neuron, not just the dendrites as **axodendritic synapses**, but also on the

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## Introduction cont'd...

### ⌚ **Synapses can be ;**

- “Asymmetric” when communication is structurally designed to be in one direction; that is, anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron

Neurons are the cells of chemical communication in the brain.

Human brains are comprised of tens of billions of neurons, and each is

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linked to thousands of other neurons.

## Introduction cont'd...

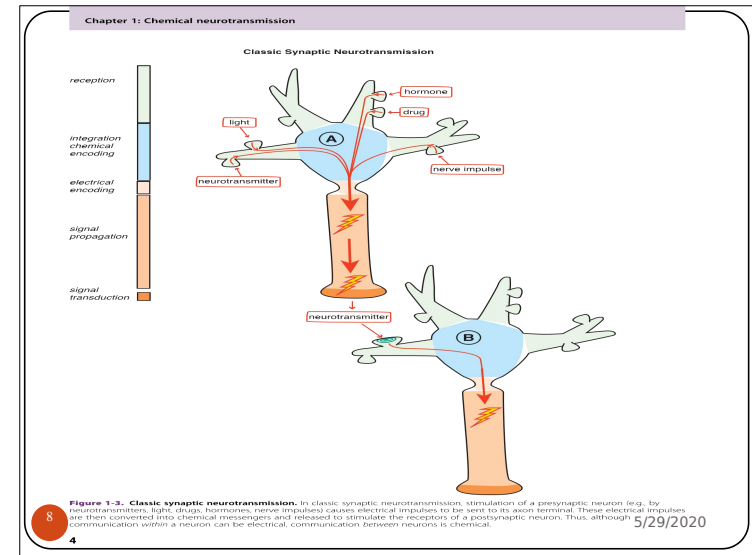
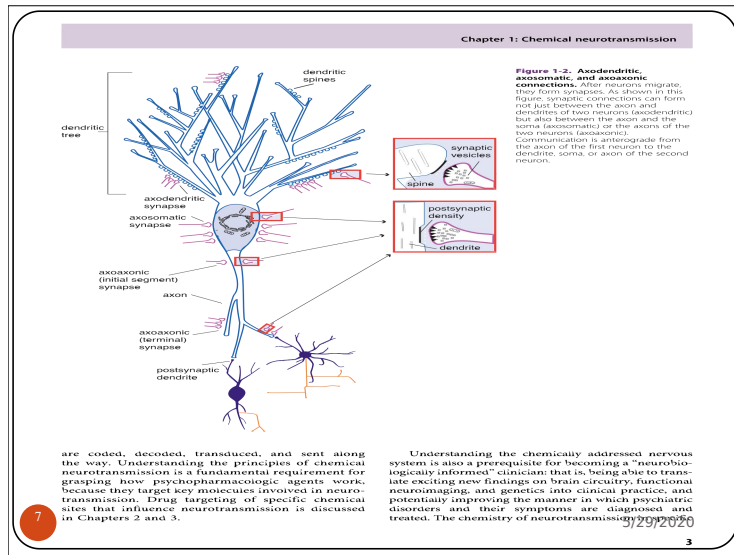
**Neurons have many sizes, lengths, and shapes that determine their functions.**

**Localization within the brain also determines function.**

**When neurons malfunction, behavioral symptoms may occur.**

When drugs alter neuronal function, behavioral symptoms may be relieved, worsened, or produced.

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## Introduction cont'd...

### Principles of chemical neurotransmission

#### Neurotransmitters

- There are more than a dozen known neurotransmitters in the brain.

#### Neurotransmission: **classic, retrograde, and volume**

Classic neurotransmission begins with an electrical process by which neurons send electrical impulses from one part of the cell to another part of the same cell via their axons.

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## Introduction cont'd...

Classic neurotransmission between neurons involves one neuron launching a chemical messenger, or neurotransmitter, at the receptors of a second .

Communication between all these neurons at synapses is chemical, not electrical.

An electrical impulse in the first neuron is converted to a chemical signal at the

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## Introduction cont'd...

Postsynaptic neurons can also **"talk back"** to their presynaptic neurons.

Which is via **retrograde neurotransmission** from the second neuron to the first at the synapse.

Chemicals produced specifically as retrograde neurotransmitters at some synapses include the endocannabinoids (EC, also known as "endogenous marijuana"), which are synthesized in the postsynaptic neuron.

Then released and diffuse to presynaptic cannabinoid .

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## Introduction cont'd...

→ Other important neurotransmitters and neuromodulators are;

→ Histamine

→ various neuropeptides and

→ hormones,

→ Some neurotransmitters are very similar to drugs and have been called **"God's pharmacopeia."**

→ For example, it is well known that the brain makes its own morphine (i.e., **β-endorphin**) and its own marijuana (i.e., **anandamide**).

→ The brain may even make its own

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## Introduction cont'd...

In addition to “reverse” or retrograde neurotransmission at synapses, some neurotransmission does not need a synapse at all!

**Neurotransmission without a synapse is called volume neurotransmission, or non-synaptic diffusion neurotransmission.**

Chemical messengers sent by one neuron to another can spill over to sites distant to the synapse by diffusion .

Thus, neurotransmission can occur at any **compatible receptor** within the diffusion 5/29/2020

## Introduction cont'd...

Modifying volume neurotransmission may indeed be a major way in which several psychotropic drugs work in the brain.

**A good example of volume neurotransmission is dopamine action in the prefrontal cortex.**

**Unlike striatum, there are very few dopamine reuptake transport pumps (dopamine transporters or DATs); to terminate the action of dopamine released in the prefrontal cortex during** 5/29/2020

## Introduction cont'd...

- Thus, dopamine is free to spill over from that synapse and diffuse to neighboring dopamine receptors to stimulate them, even though there is no synapse at these “spill over” sites .
- Another example of volume neurotransmission is at the sites of autoreceptors on monoamine neurons.
- Although some recurrent axon collaterals and other monoamine neurons may directly innervate somatodendritic receptors, these so-called somatodendritic autoreceptors

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## Introduction cont'd...

### Excitation-secretion coupling

- An electrical impulse in the first - or presynaptic - neuron is converted into a chemical signal at the synapse by a process known as **excitation-secretion coupling**.
- Once an electrical impulse invades the presynaptic axon terminal, it causes the release of chemical neurotransmitter stored there.
- Electrical impulses open ion channels - both voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs) - by changing the ionic

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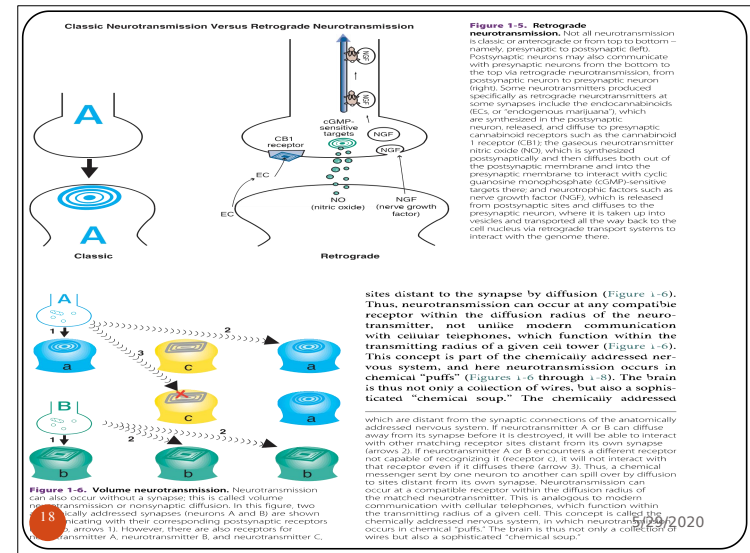
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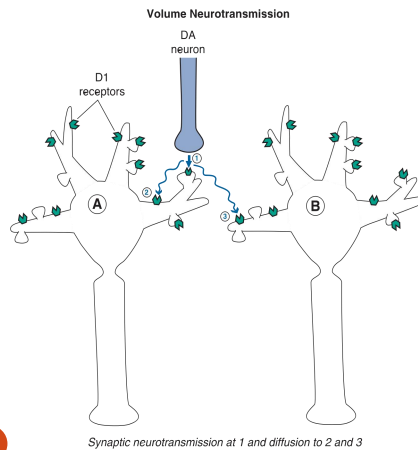
- 17 **As sodium flows into the presynaptic nerve through sodium channels in the axon membrane, the electrical charge of the action potential moves along the axon until it reaches the presynaptic nerve terminal, where it also opens calcium channels.**
- 18 **As calcium flows into the presynaptic nerve terminal, it causes synaptic vesicles anchored to the inner membrane to spill their chemical contents into the synapse.**

**Excitation-secretion coupling is thus the**

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## Chapter 1: Chemical neurotransmission



**Figure 1-7. Volume neurotransmission: dopamine.** An example of volume neurotransmission would be that of dopamine in the prefrontal cortex. Since there are few dopamine reuptake pumps in the prefrontal cortex, dopamine is available to diffuse to nearby receptor sites. Thus, dopamine released from a synapse (arrow 1) targeting postsynaptic neuron A is free to diffuse further in the absence of a reuptake pump and can reach dopamine receptors on that same neuron but outside of the synapse from which it was released, on neighboring dendrites (arrow 2). Shown here is dopamine also reaching extrasynaptic receptors on a neighboring neuron (arrow 3).

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## Summative assignment

### Essay questions.

- Discussion about signal transduction cascades.
- Explain about the roll of Forming a second messenger & the second messenger to phosphoprotein messengers ?
- Discuss molecular mechanism of gene expression.
- What are the molecular mechanisms of epigenetics ?
- Describe individual variations in drug responses.

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## Reading assignment

- *How second messenger to a phosphoprotein cascade triggering gene expression ?*
- *How neurotransmission triggers gene expression ?*
- *What is molecular mechanism of gene expression ?*
- *What are the molecular mechanisms of epigenetics ?*

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## Introduction cont'd...

### Metabolism

Drugs are swallowed, pass through stomach and are generally absorbed in the small intestine--|hepatic vein-----| liver ---| portal vein-----| systemic circulation.

The small intestine and liver are 2 groups of docking stations that are metabolic factories  
- Phase 1 and Phase 2.

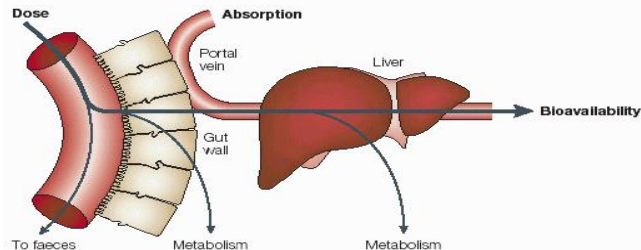
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Drug products are not transformed continually through the gut.

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## Introduction cont'd...

- Uptake of orally administered drug proceeds after the stomach passage via the small intestine.
- In the gut and liver, a series of metabolic transformation occurs

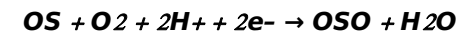


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## Phase 1 and Phase 2

- Phase 1 -introduces oxygen to provide a "chemical handle" --I drugs become more hydrophilic (so it can be handled by the kidney or biliary system) and start to be inactivated by (e.g. esterases, cytochrome phosphates (CYPs).
- The most common reaction catalyzed by cytochromes P450 is a mono-oxygenase reaction, e.g. insertion of one atom of oxygen into an organic substrate (OS) while the other oxygen atom is reduced to water:



- Phase 2 uses the handle to allow enzymes called transferases to hook up to Phase 1

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## Introduction cont'd...

### What are CYPs?

- Superfamily of heme-containing enzymes
- Two kinds, some in **mitochondria** that chew up **endogenous** products (e.g. **steroids**) and some in the **endoplasmic reticulum** that chew up **drugs, foods, herbals, toxins**

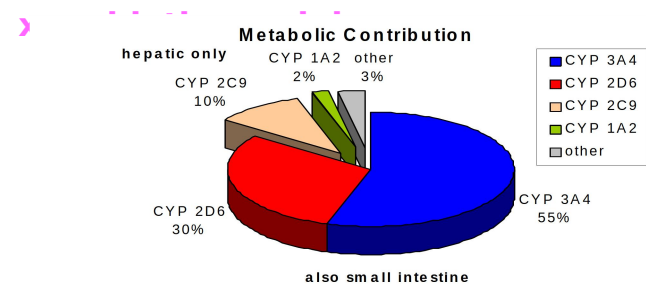
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## Introduction cont'd...

### Cytochrome P450 enzymes

Especially CYP 3A4, CYP 2D6, and CYP 2C9 are involved in the metabolism of



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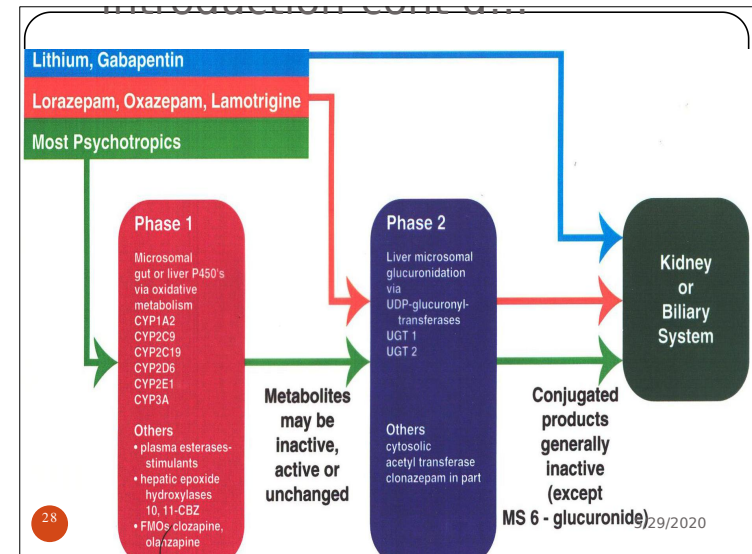
## Introduction cont'd...

### CYP Genetics

- ⌚ If the CYP docking site is “faulty” so that Drug C can’t dock--| higher systemic plasma concentrations (Slow metabolizer)
- ⌚ If there are multiple copies of the docking site (more on line), Drug C is metabolized more efficiently--| lower plasma concentration (Ultra-rapid metabolizer).

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## Naming of Cytochrome P450s(CYP450)

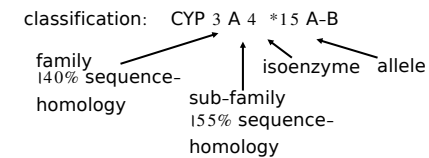
- Ø CY (first 2 letters)---P (protein) and 450--- (from the observation in the lab of the wave length of absorption when CO infused).
- Ø Nomenclature was invented to describe the relationship of CYPs to each other-- no clinical significance
- Ø Amino acids of each CYP elucidated & a nomenclature based of how similar CYPs are to each other.

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## Cytochrome P450 Naming

### Cytochrome P450 Naming



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## Which CYPs are important in drug metabolism

- ✿ CYP1A2-chromosome 15
  - ✿ CYP2C9-chromosome 10\*\*
  - ✿ CYP2C19-chromosome 10\*\*
  - ✿ CYP2D6- chromosome 22\*\*
  - ✿ CYP2E1-chromosome 10
  - ♣ CYP3A (4/5/7)-chromosome 7
- \*\* most genetic information

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## P450

CYP is a large and diverse group of enzymes  
function of most CYP enzymes is to catalyze the oxidation of organic substances

CYPs are the major enzymes involved in drug metabolism and bio activation, accounting for ~75% of the total metabolism.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozymes (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug

interactions.

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## GENERAL PRINCIPLES of neural transmission

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### Objective

1. Understand the general mechanisms/concepts of **neural transmission**
2. Describe the major Neurotransmitters - **Synthesis, break down, receptors, and distribution** in the CNS
3. Explain the **functional significance** of neurotransmitters within the nervous system, and their relevance to both **normal and abnormal behavior**

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→ Neural transmission is a biochemical process, carried out by a variety of *neurotransmitter* and *neuromodulator substances*.

↓ These *substances* *diffusion of across the synaptic clefts* that separate individual neurons.

↓ Permits one individual neuron to be able to *communicate* with the next.

↓ Allow for communications among *diverse regions* of the nervous system necessary for the integration of *different functional units* required in complex behaviors.

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→ Neurotransmitters and neuromodulators comprise an *integral part of behavioral neurology and neuropsychology*.

→ The major neurotransmitters in the central nervous system:

- Acetylcholine(ACH)
- Glutamate(GU)
- Gamma-amino butyric acid(GABA)
- Epinephrine/Norepinephrine(E/NE)
- Dopamine(DA)
- Serotonin(5-TH)

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→ **Propagation of a Nervous Impulse** (“action potential”) along a neuron is the result of a progressive, sequential depolarization along the axon.

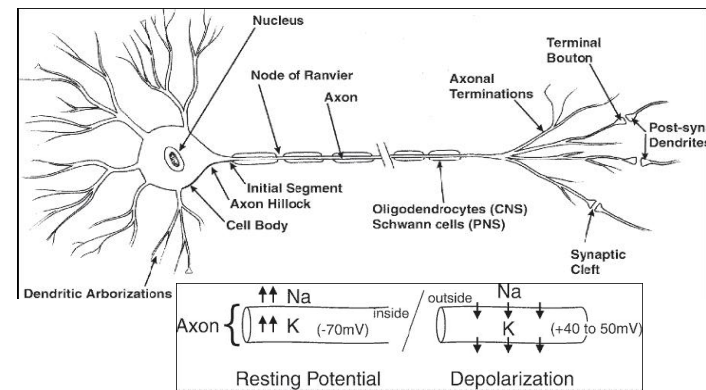
“ Depolarization is characterized by an **influx of sodium** ( $\text{Na}^+$ ) ions and the subsequent **efflux of potassium** ( $\text{K}^+$ ) ions across the cell membrane via the opening of voltage-gated ion channels

“ The ligand-gated ion channels are directly or indirectly **activated by the action of neurochemical transmitters** at the chemical synapse.

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## GENERAL PRINCIPLES cont'd...



- **Basic components of a neuron; Major changes that take place in the axon during an axon potential**

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## Production and Storage of Neurotransmitters

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### → Production and Storage of Neurotransmitters

- ” Neurotransmitters are synthesized by enzymes within the **presynaptic terminals** and stored in **presynaptic vesicles**,
  - Other neurotransmitters, such as acetylcholine, are synthesized elsewhere in the cell and subsequently transported into their vesicle.
- ” A given presynaptic terminal may synthesize, store, and release **multiple neurotransmitters**.

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### Events at presynaptic terminal

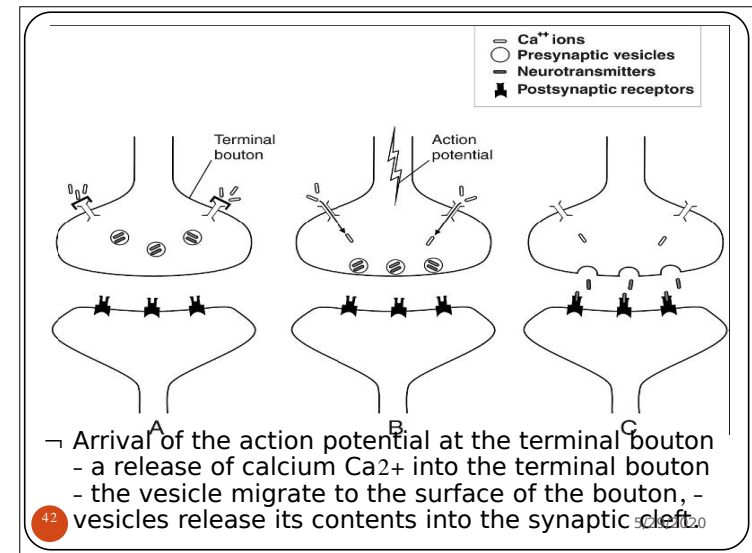
When the action potential of the neuron reaches the presynaptic terminal

An influx of calcium ( $\text{Ca}^{2+}$ ) ions into the terminal, depolarizing it.

Vesicles are transported to presynaptic membrane

Discharge their contents (i.e., neurochemical transmitters) into the synaptic cleft.

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## Neurotransmitter Receptors

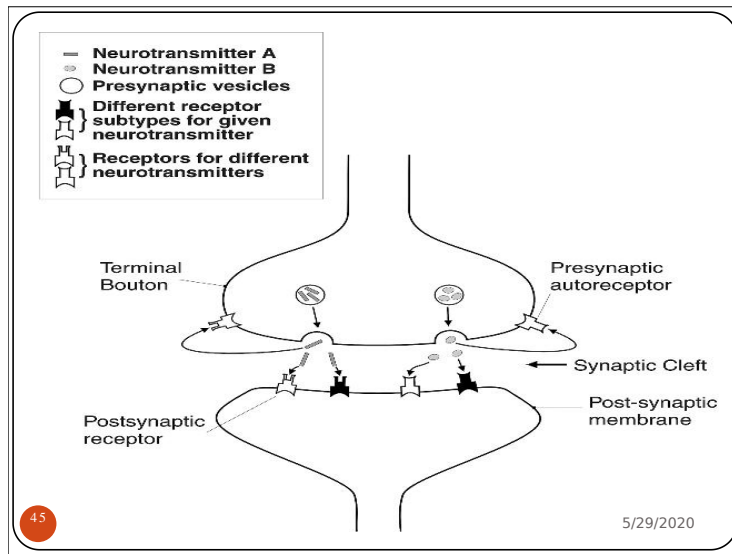
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- Receptors are strings of specially designed proteins
- Each neurotransmitter has its own unique set of receptors into which it fits.
- Each neurotransmitter generally has multiple receptor subtypes.
  - just as a master key may open several different locks.
- Various receptor subtypes may be found at a single synapse.

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→ **Receptors** are manufactured within the endoplasmic reticulum and Golgi apparatus of the neuron.

Neurotransmitters act by binding to a particular receptor after they are released

The receptor initiates a secondary response

Leads to any one of several **cellular events**

Leads to some behavioral change

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" **Cholinergic** nicotinic receptors typically are associated with preganglionic neurons of;

- the **sympathetic** nervous system
- the **parasympathetic** nervous system and
- **somatic muscle** innervation

" Muscarinic receptors, also responsive to acetylcholine, are found

- i at the end organs innervated by postganglionic **parasympathetic** fibers

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" Different receptors subtypes, even though stimulated by the **same neurotransmitter**,

- may result in a very different behavioral response, both clinically and at the cellular level

" Either **too much** or **too little** release of a neurotransmitter at the synapse;

- associated with **behavioral dysfunction.**

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- **G-Protein-Linked vs. Ligand-Gated Ion Receptors**
- **Allosteric Modulation**
- **Autoreceptors**
- **Heteroreceptors**
- **Receptor Regulation**
- **Neurotransmitter Degradation/Reuptake**
- **Drug actions**
  - a. **Drug-Receptor Interactions**
  - b. **Enzymatic Actions**
  - c. **Reuptake inhibition**
- **Side Effects and Receptors**

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## **G-Protein-Linked and Ligand-Gated Ion Receptors**

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- ✓ **Receptor superfamilies** - represent more generic classes of receptors that cut across individual neurotransmitters.
- ✓ **Two major subtypes** are defined: These two types of receptors differ both structurally and functionally
- 1. **G-protein-linked receptors**-*metabotropic* produce their effects via different mechanisms; do not have a direct impact on ion channels  
*slow acting neurotransmitters*-the monoamine transmitters (DA, NE, 5-HT),

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### → In G-protein receptors;

- ò Binding of the neurotransmitter ('first messenger') to the receptor causes a conformational change in the receptor.
- ò Enables it to bind with a G protein inside the cell Membrane.
- ò Leads to the activation of an intracellular enzyme.
- ò Produces a 'second messenger.'

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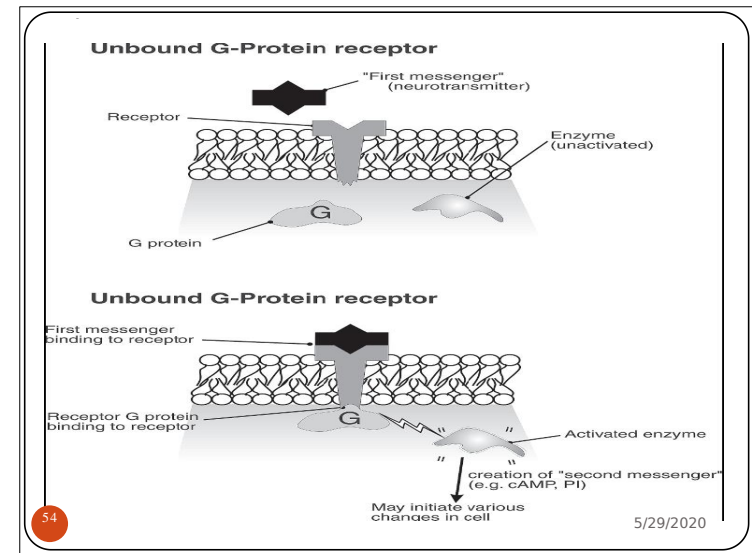
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ò This **second-messenger** effect any number of changes within the cell or may impact directly on other receptors.

1. **Activating other enzymes.**
2. Impacting on the DNA of the cell, which in turn may set in motion the **synthesis or degradation of other enzymes and proteins** (including receptors).
3. Modulation or “opening” (through phosphorylation) of **ion channels**.

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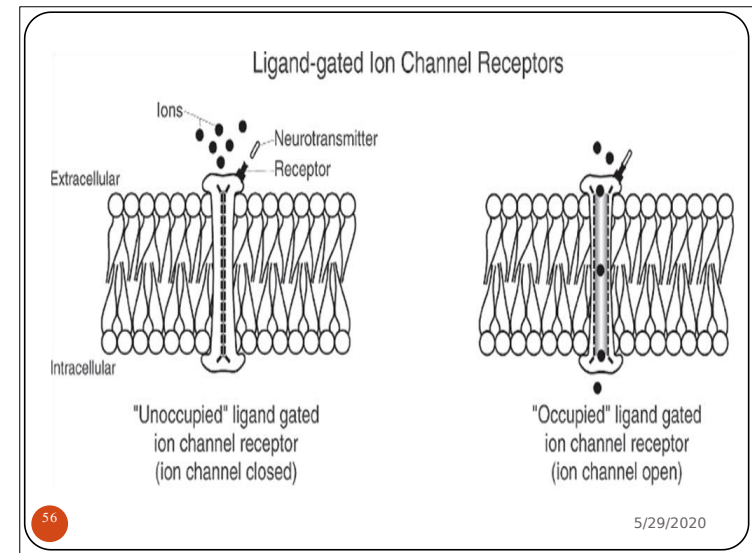
## 2. **Ligand-gated receptors** (*ionotropic*)

- When stimulated by an agonist or neurotransmitter they alter (increase) the flow of ions through the channel.

↳ amino acid transmitters glutamate and GABA-*fast-acting* neurotransmitters

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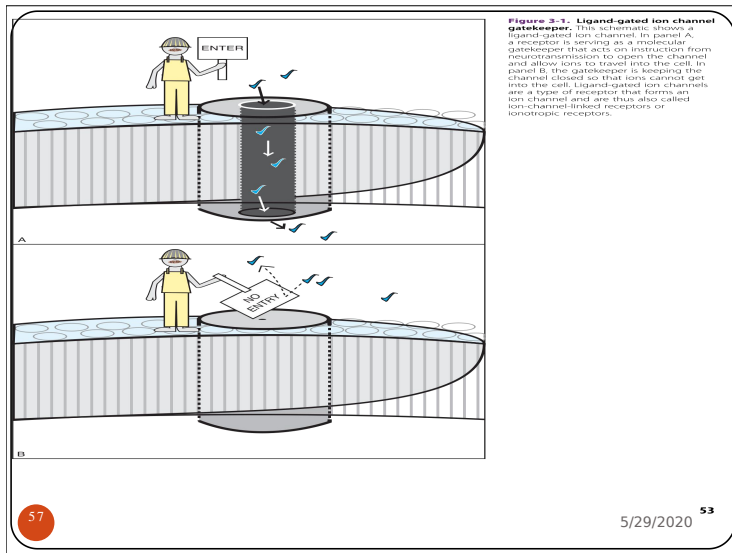
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- ⌚ Each synapse may have **receptors** that are **responsive to more than one** type of neurotransmitter.
- ⌚ Single receptors may have **multiple binding sites** that are responsive to **different chemical molecules**.
- ⌚ For example, a primary receptor for neurotransmitter A might have sites that also are responsive to neurotransmitter B.

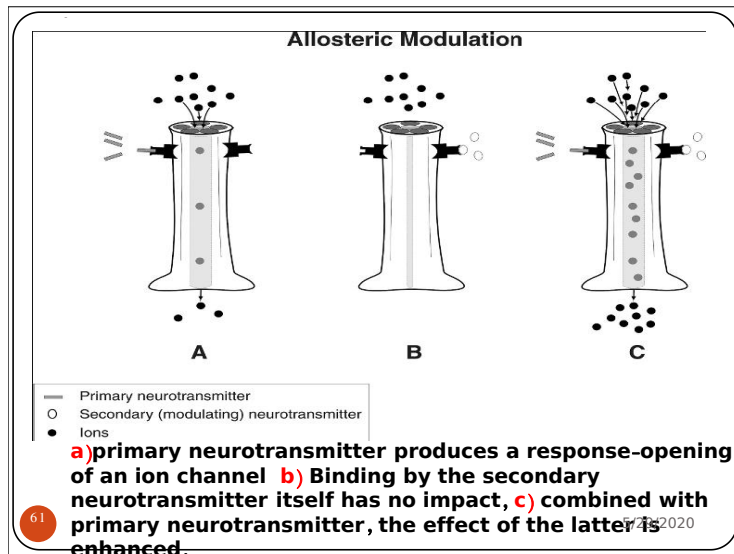
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- ⌚ These **secondary neurotransmitters** or **“modulators”** (e.g., neurotransmitter B) are unable to effect a response independent of the primary neurotransmitter.
- ⌚ They can alter significantly the response of the receptor once the primary neurotransmitter adheres to its binding site. This process is known as **allosteric modulation**

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Allosteric modulation may be either **positive** or **negative**

If positive, the effect of binding by these secondary transmitter substances will be to **enhance or augment the effect** produced by the primary neurochemical transmitter.

Negative allosteric modulation, by contrast, would **reduce or possibly even reverse** the normal response elicited by the

– **Positive allosteric modulation**

e.g. the GABA receptor (specifically, the GABA-A receptor) is responsible for controlling the flow of chloride ( $\text{Cl}^-$ ) ions into the intracellular space.

- ò When GABA binds to these receptors, it facilitates the opening of these **chloride channels**.
- ò When benzodiazepines or barbiturates bind to the GABA-A receptor in the presence of GABA, they respectively **increase the frequency and the length of time the channel remains open**

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## Autoreceptors

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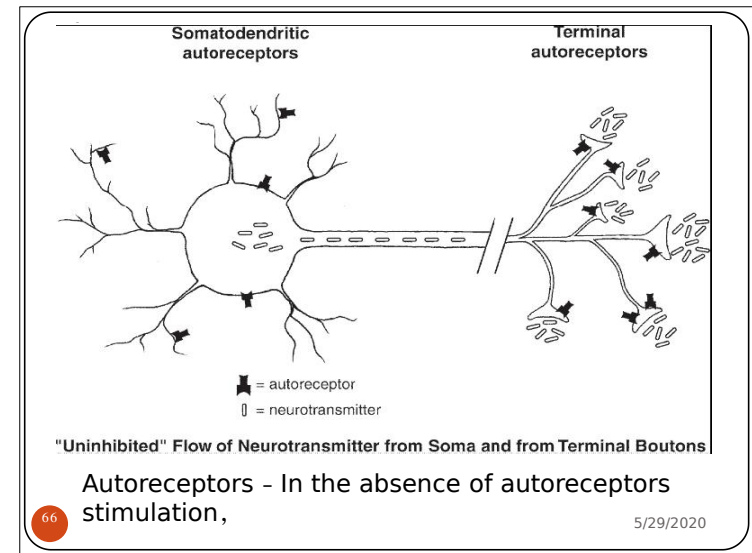
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- Not all receptors are located on the postsynaptic membrane.
- Receptors sensitive to the released transmitter commonly are found either on the dendrites (or cell body itself) or at the same presynaptic terminal from which the neurotransmitter was released. These may be .
  - an integral part of the **reuptake transport**
  - serve as **feedback receptors** for neurochemical transmitters within a particular cell.

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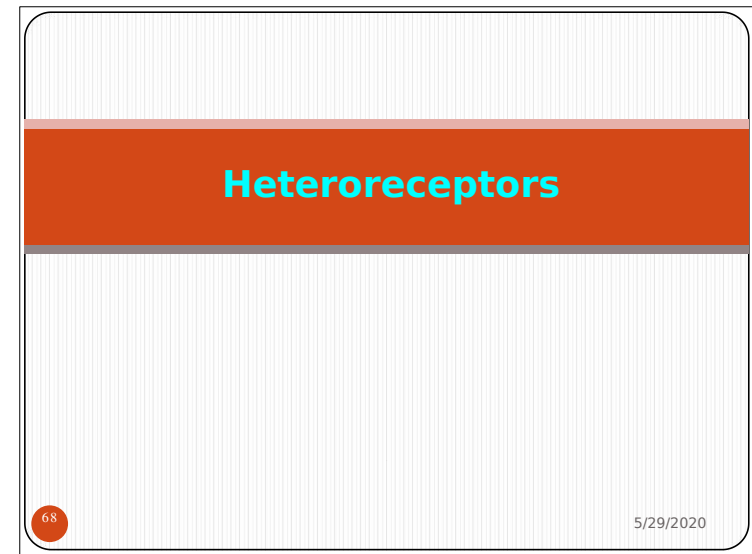
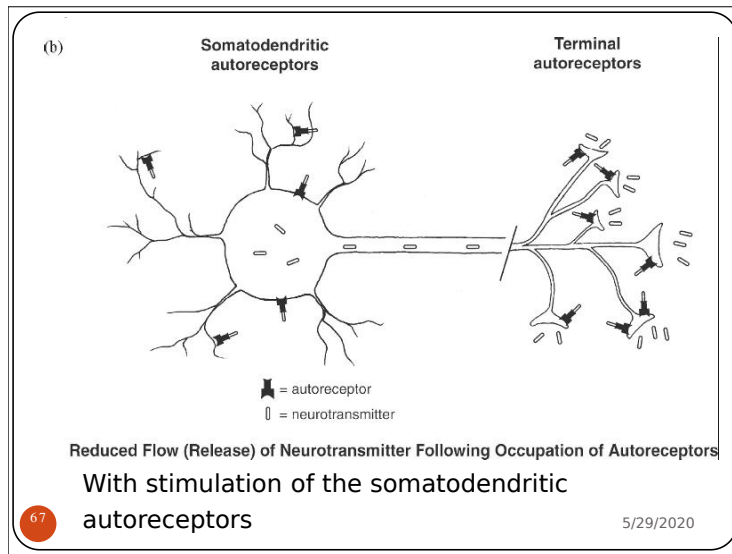
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Insofar as they mediate the latter function



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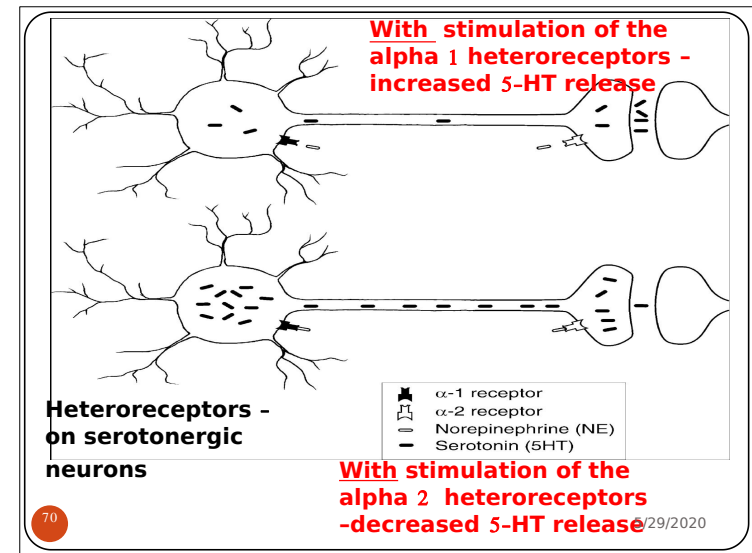
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- ⓐ A neurotransmitter not only may affect its own release via autoreceptors,
- ⓐ Some diffuse to their own receptors located on other neurons, where it **either inhibit or facilitate release of a second neurotransmitter**.
- ⓐ Because of this heteromodal influence (i.e., over different neurotransmitters), such receptors are known as **heteroreceptors**.  
e.g.
  - └ **Alpha-1 receptors** - located on the cell bodies of **serotonergic neurons**. When stimulated **facilitate the release of 5-hydroxytryptamine (5-HT) (serotonin)**.
  - └ **The opposite occurs when norepinephrine stimulates the alpha-2 receptors** located on the terminals of 5-HT neurons - the release of serotonin is

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- **Serotonin**, on the other hand, via 5-HT<sub>2A</sub> heteroreceptors located both on terminal and somatodendritic and portions of dopaminergic neurons can **inhibit the release of dopamine**.

e.g., the atypical antipsychotics **block** these 5-HT<sub>2A</sub> **heteroreceptors**.

- Increase the release of dopamine in certain areas of the brain,
- Can decrease the side effects - associated with traditional antipsychotics [e.g., by increasing the release of dopamine (DA) in the **nigrostriatal system**]
- Improve the “negative” symptoms of schizophrenia (by increasing DA **in the frontal regions- mesocortical**).

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## Receptor Regulation

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## Regulation of the synthesis of receptors

### Up-regulation of receptors

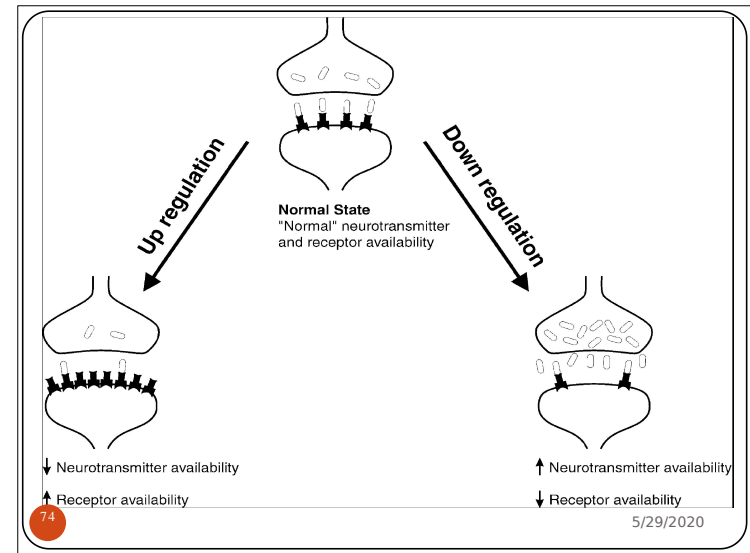
When there is relative deficiency of a particular neurotransmitter at a given synapse the cell produce more receptors.

### Down-regulation of receptors

If there is too much of a neurotransmitter – the cell reduce the number of its receptors.

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## Neurotransmitter removal

Degradation  
Reuptake  
Diffusion

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- u A neurotransmitter needs to be cleared from the synapse, once it carry out its intended activity,
  - l Prevents the possibility of **tonic stimulation** of the postsynaptic membrane or presynaptic autoreceptors.
  - l **Prepares the synapse** for the next stimulus generated by the presynaptic neuron.

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– Three basic possibilities as to how this might be accomplished:

- ♣ Neurotransmitter might be **degraded by enzymatic action** while still in the synaptic cleft.

- ♣ **“Transported” back** into the presynaptic terminal.

- | simply returned to the presynaptic vesicles where it is again stored until needed.

- ♣ Simply **diffuse away** from the synaptic cleft.

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### a. Degradation

– Different enzymes are involved in the breakdown of different neurotransmitters.

- Ⓢ *Catechol-*o*-methyltransferase (COMT)* - degradation of NE and DA.

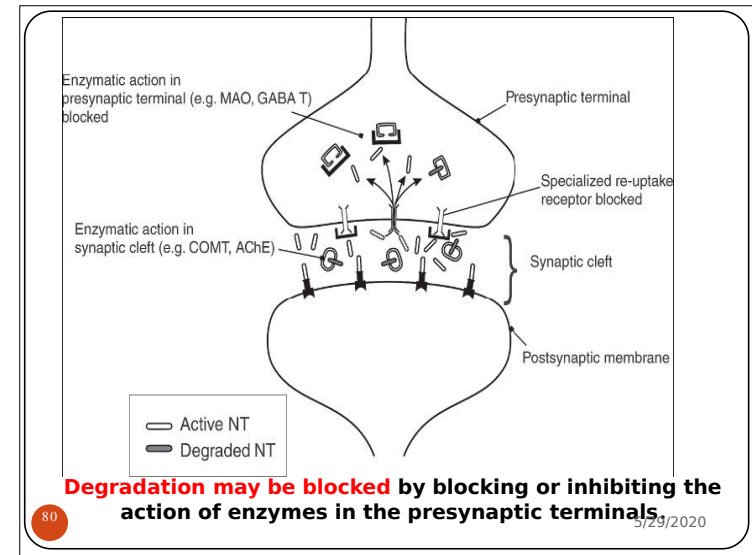
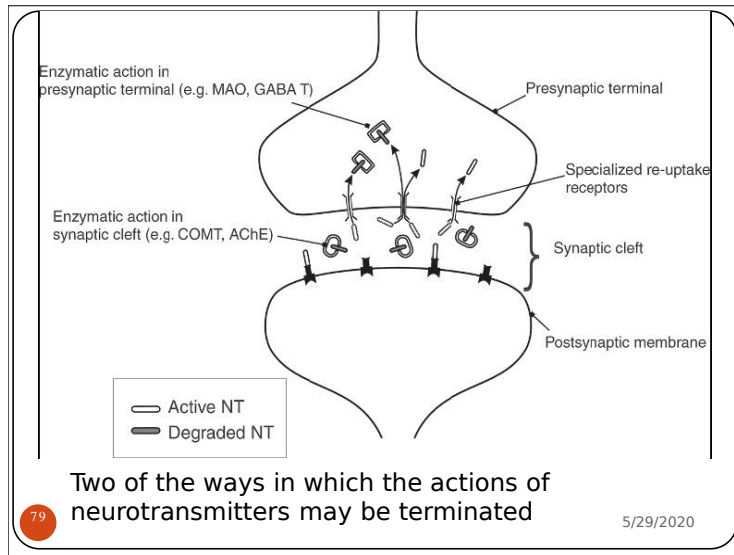
- Ⓢ *Acetylcholinesterase (AChE)* - acetylcholine down into choline and acetate

- Ⓢ *Monoamine oxidase (MAO)* -destruction of NE, DA, and 5-HT

- Ⓢ *Gamma-aminobutyric acid transaminase (GABA-T)* - break down of GABA.

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### b. Reuptake

- To terminate the activity of a neurotransmitter in the synaptic cleft -to shepherd it back into the synaptic terminal from which it came.
- Accomplished by yet another specialized chain of proteins known as *transport pumps*, *reuptake proteins*, or *transport carriers*.

### c. Diffusion

Glutamate is transported back into either the presynaptic terminal or the neighboring glial cells.

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## Drug actions

- a. Drug-Receptor Interactions
- b. Enzymatic Actions
- c. Reuptake inhibition

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### a. Drug-Receptor Interactions

- Neurotransmitters are not the only substances that can bind to receptor sites.
- Many drugs, various toxic agents, and a host of other psychoactive substances.
- ” produce their effects through their capacity to occupy specific receptors.

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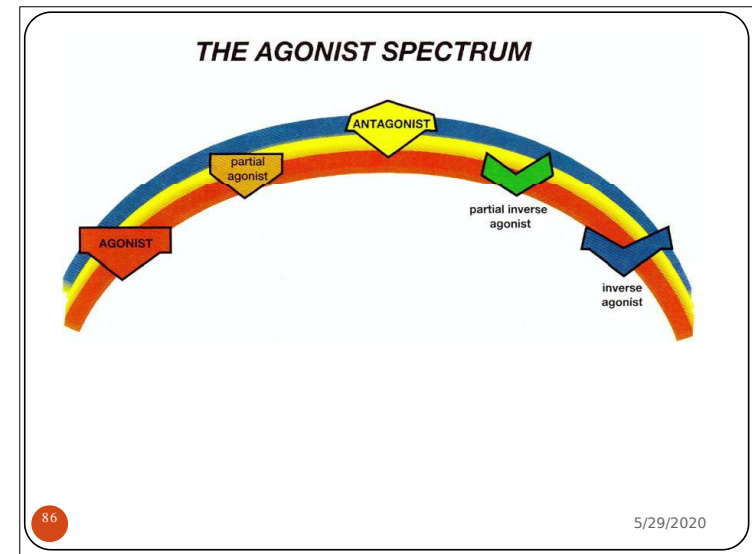
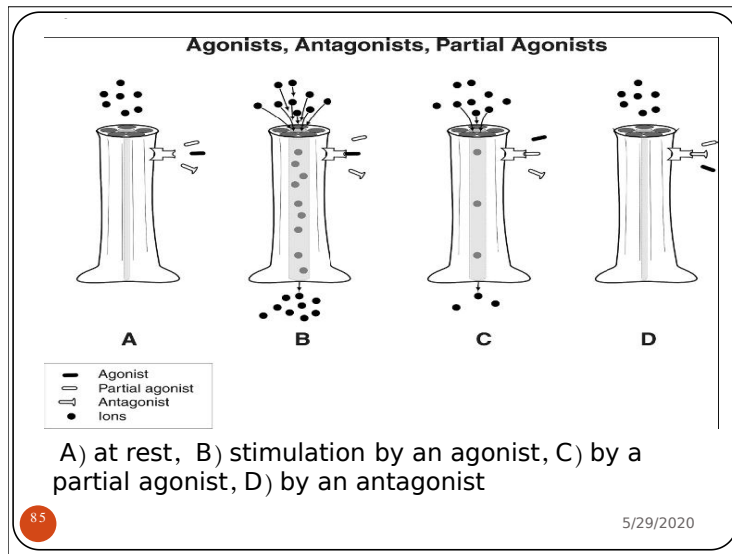
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@ These drugs can impact on receptors in a variety of ways. The most commonly known mechanisms are as

- **Agonists**- any substance that activate the receptor.
- **Antagonists**- simply blocks the receptor site, preventing an agonist (or other substance) from binding at that site.
- **Partial Agonists** - either as a partial agonist or as a partial inverse agonist.

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## b. Enzymatic Actions

- In order to carry out the normal activity of the enzyme, the cell must synthesize new enzymes.
- @ Antagonist drugs also may **block** the actions of enzymes.
- @ Different drugs might act as either ***reversible or nonreversible inhibitors of enzymes.***

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- Certain disease states -associated with neurotransmitter deficiencies.
  - } **Alzheimer's disease -acetylcholine deficiencies.**
  - } **depression -monoamines deficiencies.**
- Drug treatments may be designed to inhibit these destructive enzymes, thus increasing the supply of the neurotransmitter.

## C. Reuptake inhibition

- ò Inhibits the reuptake of a neurotransmitter from the synaptic cleft back into the presynaptic terminal button,
- ò Increased amount of the neurotransmitter in the synaptic space,
- ò Therapeutic effect.

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- When certain molecules bind to these protein strings (i.e., the transport pumps),
  - Effect a change in the configuration of the protein molecules that in effect **precludes the binding of the neurotransmitter**.
  - They cannot bind to the carrier and they cannot be transported into the cell.

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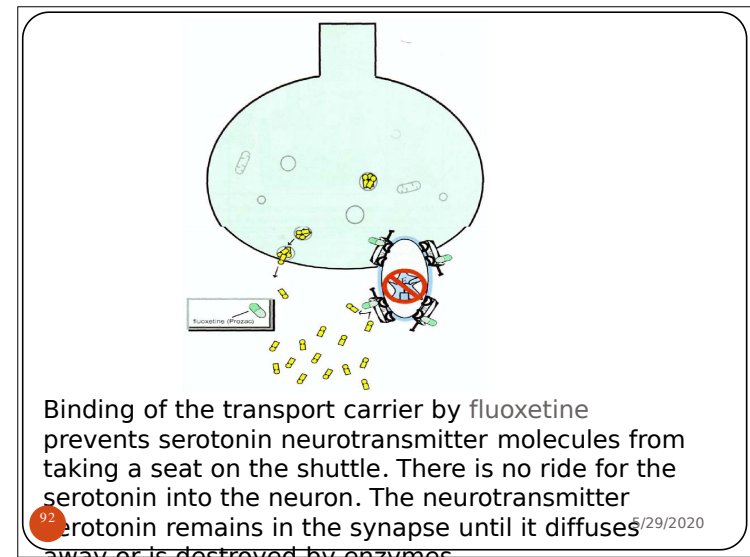
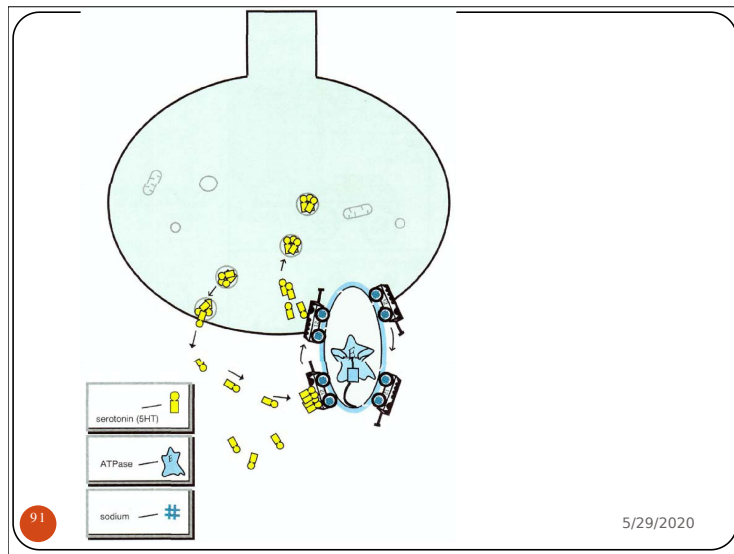
Cannot be transported back into the presynaptic terminal, they must remain in the synaptic cleft.

- ┌ Either slowly diffusing away from the synapse .
- ┌ Awaiting enzymatic catabolization in the synaptic cleft itself.
- ┌ This results in an **increased supply of neurotransmitter** substance in the synapse.

This basically is the principle by which the **selective serotonin reuptake inhibitors (SSRIs)** operate.

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## Drug Side Effects and Receptors

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Side effects generally result from the fact that a given medication either acts on:

1. Receptors other than the one(s) primarily targeted,
2. Receptors (of the targeted transmitter) that may be present in organs or functional systems other than the one(s) intended.

Drugs often have the capacity to bind to various classes of receptors.

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**e.g. tricyclic antidepressants**

- Block monoamine (primarily NE and 5-HT) reuptake at the synapse.
- Block M1 (cholinergic)
- Block alpha 1 (adrenergic)
- Block H1 (histaminic) receptors

@ Neuroleptic medications (typical) have similar, undesirable side effects

- Blocking mesolimbic pathways
- Blocking dopaminergic receptors in the nigrostriatal, tuberoinfundibular, and mesocortical pathways

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THANK YOU

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